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THE SURGICAL SIGNIFICANCE OF ACUTE ABDOMINAL PAIN*

J. William Hinton, M.D.†

NEW YORK CITY

IN REVIEWING case records in two of the larger hospitals of New York over a period of twenty-seven years, I have been disturbed by the frequency with which patients suffering from acute abdominal pain are subjected to laparotomy with resulting negative pathological findings. Even more distressing is the opinion expressed by many surgeons that exploration with negative findings is preferable to unrecognized acute appendicitis, which may develop into peritonitis with a fatal termination. One cannot but question this attitude in view of the present minimal mortality rate from acute appendicitis, including cases with abscesses and general peritonitis.

A review of acute appendicitis on the Fourth Surgical Division of Bellevue Hospital over a twelve-year period (1928 to 1939, inclusive) demonstrated the following mortality rate during the first six years[1]: 6.3 per cent in 1928 to 1933, and 3.4 per cent in 1934 to 1939, inclusive. The total mortality of 677 patients suffering from acute appendicitis was 5.1 per cent. The diagnosis was based entirely on the findings of the pathologist and not on those of the operating surgeon. Among these 677 patients, there were 474 cases of unruptured acute appendicitis, 67 cases of localized peritonitis, 88 abscesses and 48 cases of general peritonitis. In 75 per cent of the cases, the operations were performed by the house staff, and the junior attending staff performed the other 25 per cent. These statistics represent the results before chemotherapy was instituted.

From 1940 to 1948, inclusive, there were 320 operations for acute appendicitis with the same percentage of peritonitis and abscesses, and the resident staff performed 98 per cent of the operations. There were 4 deaths, 3 of which were caused by cardiac insufficiency. This is a mortality of 1.2 per cent, which eliminates the great fear of death from acute appendicitis. Reasons for the diminished mortality include the use of chemotherapy, the more frequent use of plasma and blood and keeping the patient well hydrated at all times. Improved anesthesia and a better trained resident and nursing staff are important advances.

Dr. Edgar Burke,[2] surgical director of the Jersey City Medical Center, reported for 1947 a total of 271 cases of acute appendicitis, including those with general peritonitis, local peritonitis and abscesses, and of this number, there was 1 death, or a mortality of 0.36 per cent.

The mortality in children with acute appendicitis should be compared with the adult statistics. The Children's Surgical Service, which is a subdivision of the Fourth Surgical Division of Bellevue Hospital, has had from 1928 to 1947, inclusive, 1165 operations for appendicitis, with a total mortality of 3.8 per cent. Of these, there were 70 per cent unruptured and the other 30 per cent divided between abscess and general peritonitis. The adult service had 997 cases of acute appendicitis from 1928 to 1948 inclusive, with a total mortality of 4 per cent. There is thus no appreciable difference in the mortality rate in the age groups when statistics from the same institution, a municipal hospital, are compared.

The teaching of three or four decades ago was to impress upon the clinician that acute abdominal pain represented an acute pathologic process that usually necessitates a laparotomy. Medical students were told that the appendix was the most frequently diseased organ they had to fear. This teaching has become so thoroughly implanted in the mind of the surgeon, and to a great extent in the mind of the internist, that a patient suffering from acute abdominal pain is usually regarded as a candidate for laparotomy. Frequently, the laparotomy reveals negative findings.

Certainly, a patient with acute abdominal pain should not be rushed into a laparotomy unless there are clear-cut indications that a real pathologic process is present.

Acute abdominal pain may be attributed to three causes: anxiety neurosis with conversion symptoms or other psychogenic factors; physiologic conditions, such as painful ovulation, more frequently referred

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†Director, Fourth Surgical Division, Bellevue Hospital; director, Surgical Service, New York University-Bellevue Medical Center.

to as intermenstrual pain or Mittelschmerz; true organic diseases that require surgical care.

It is the first two groups that I wish to discuss first, to emphasize their importance in the differential diagnosis of acute abdominal pain that may necessitate a laparotomy.

Conversion symptoms, the emotional or psychogenic cause of abdominal pain, are the type most frequently overlooked. This is apparently due to the fact that most surgeons have been taught that any acute abdominal pain represents true organic disease and therefore necessitates laparotomy. This teaching is not only erroneous but also tragic for the patient who submits to laparotomy because of psychosomatic symptoms. The question is asked, Can true pain exist without some underlying pathologic condition? Miller[3] states, "May I suggest humbly that pain is what the patient thinks it is and the only clue we have as to whether the patient feels the pain is what the patient says about it."

Bennett and Semrad[4] reported that among 100 patients with psychoneurosis admitted to a university hospital, organic disease, including gastrointestinal disease, hyperthyroidism, organic cerebral disease and other conditions of vital importance, was diagnosed in 72. One hundred and seventy-nine operations had been performed, at least half of them unnecessarily. Of these 100 patients, 70 showed satisfactory and lasting improvement under psychotherapeutic treatment. Bennett[5] more recently reviewed the histories of 121 women on whom 205 operations had been performed: 159 major and 84 pelvic procedures, 40 appendectomies, 11 gall-bladder and 16 thyroid operations, 5 postoperative adhesions, 3 kidney operations, 46 minor operations, 12 rectal procedures, 24 on tonsils and nasal sinuses, and 1 for varicose veins. He stated that it was hard to determine how many were necessary, but in the majority of cases the patient agreed to the operation with the understanding that it would bring relief from the nervousness, although the chances are that none of the operations were indicated from that point of view.

The fact that so many patients presenting pain due to psychogenic conditions are subjected to unnecessary operations reflects on the teaching, either in medical school or during a residency. Apparently, too much emphasis is placed on diagnostic laboratory procedures and too little on clinical evaluation of the history. I am not a psychiatrist and have never had psychiatric training, but I believe that most physicians can suspect the presence of a functional disorder merely by allowing the patient to talk and get his history as he presents it without interruption. The history is one means by which psychogenic pain may be suspected and then confirmed or ruled out by a psychiatric consultation.

A number of years ago the physician with whom I was discussing the end results of operations on patients with poor psychiatric backgrounds told me the following incident. A well known surgeon had consented to perform a laparotomy on a patient because she insisted that she had a frog in her stomach. At first he tried to dissuade her, but finally he decided to perform the laparotomy and present her with a frog. This was done, and the patient was asymptomatic for six months. She then returned and demanded a second laparotomy because of the fact that frog's eggs had been left in her stomach at the time of the original operation. I do not have a further follow-up record on this patient, but I do not believe one has to stretch one's imagination to guess the end results of such a procedure.

Wearn,[6] in his chairman's address before the Section of Internal Medicine of the American Medical Association in 1947, stated:

> Of some 15,000,000 men examined by Selective Service, 1,875,000 were rejected on the ground of neuropsychiatric disorders. This represents 37 per cent of the men rejected for all causes; and even after this initial screening, 39 per cent of all medical discharges from the army between January 1942, and December 1945, were classified as psychoneurosis. At least 5 out of every 10 patients who consult physicians today prove through examination to have no organic basis for their complaints.

Acute abdominal pain is frequently caused by painful ovulation that is not recognized by the surgeon or by the attending physician. It usually occurs in the younger woman in the twenties or early thirties. This condition is also known as intermenstrual pain or Mittelschmerz. A characteristic point in the history is that the pain occurs ten to twelve days before menstruation. There may be also evidence of scant vaginal bleeding at that time.

This condition has been known for over a century — Pouchet, in 1847, discussed it in a book on ovulation and conception in mammals. Sir William Priestly, in 1782, and Howard Kelly, of the United States, discussed the condition frequently. The diagnosis should not be difficult if one keeps the possibility in mind and elicits a careful history. Many a patient will volunteer the information that the pain occurs ten to twelve days before menstruation and occurs regularly. There are no constant pathological findings in intermenstrual pain either microscopically or macroscopically. There is no unusual thickening of the ovarian capsule, which has been suggested as a possible cause of pain. The physiologic nature of the disorder does not interfere with reproduction, and it is never a cause of sterility. The pain is not permanent and, in many cases, disappears without any form of treatment.

There is real danger of abdominal hemorrhage resulting from a ruptured graafian follicle or cyst of the corpus luteum. The hemorrhage may be quite profuse in the peritoneal cavity and may

cause a difficulty in ruling out rupture with ectopic pregnancy — a diagnosis that is frequently made by error. A laparotomy is indicated in severe hemorrhage from a ruptured cyst as well as in a rupture with ectopic pregnancy. Sackett[7] has reviewed the subject of intraperitoneal hemorrhage of ovarian origin, and his bibliography is most exhaustive on this type of hemorrhage. In the majority of hemorrhages from a graafian follicle or cyst of the corpus luteum there is no free bleeding in the peritoneal cavity; if present, it is minimal in amount. The pain is caused by distention of the follicle or cyst.

In the treatment of intermenstrual pain laparotomy should be avoided in the absence of profuse bleeding in the peritoneal cavity, and these constitute by far the majority of cases. There is no specific medication or treatment for recurrent attacks of pain except rest. The patient usually finds that rest in bed for a day or so greatly diminishes the severity of the pain, which subsequently disappears spontaneously.

Follow-up observations on the results of laparotomy performed for psychogenic causes or intermenstrual pain show that the procedure is unsatisfactory and frequently harmful. Some patients may have eight or ten laparotomies and often become addicted to the use of morphine. In others intestinal obstructions may develop, necessitating one or more operations for correction, and deaths occur in these cases.

The true organic lesions causing acute abdominal pain in their order of frequency are acute appendicitis; intestinal obstructions, whether from neoplasm of the large intestine, intussusception, volvulus or mechanical obstruction of the small gut from bands or adhesions; perforated ulcer of the stomach or duodenum; acute cholecystitis; torsion of ovarian cyst or pedunculated fibroid; torsion of the omentum; and rupture of viscera due to trauma of the abdomen.

In these conditions the diagnosis needs no detailed discussion, since the symptoms and the physical and laboratory findings are well known to both the internist and the surgeon. Treatment is usually surgical operation either during the acute stage or as an elective procedure. If an operation is to be performed during the acute stage, the patient should be well hydrated before laparotomy is done. If the patient has been ill from peritonitis for forty-eight, seventy-two, or ninety-six hours, it may be better to delay the operation for twelve to twenty-four hours so that a fluid balance can be established, and, of course, chemotherapy is instituted immediately.

Cases of acute intestinal obstruction should receive special mention in view of the rather general use of the Miller–Abbott tube. I refer to mechanical obstructions, not those of the adynamic or paralytic type. From my observations at Bellevue Hospital, which has an active ambulance service, tumor of the large intestine and strangulated hernia are the most frequent causes of mechanical intestinal obstruction. The treatment of the latter is obvious, and an operation should be performed as soon as hydration permits. Unfortunately, patients with tumor of the large intestine causing complete obstruction have been and are still being treated with a Miller–Abbott tube for decompression purposes. This practice should be completely condemned. There is no place for the Miller–Abbott tube in the management of obstruction of the large intestine. Surgical decompression is required in these cases as soon as the general condition of the patient permits. In the treatment of complete obstruction of the small intestine, use of the Miller–Abbott tube should be abandoned. This is also a surgical problem and should be so handled.

The Miller–Abbott tube has a therapeutic place in cases in which partial obstruction has developed after recent laparotomy. Fresh adhesions may not need a second laparotomy if the intestine can be kept decompressed for several days. The Miller–Abbott tube has a place also in the treatment of adynamic or paralytic ileus.

I should like to mention briefly the significance of abdominal pain due to femoral or inguinal hernia. A small hernia may cause partial or complete obstruction of the small intestine. The hernia may be so small that it is overlooked on physical examination and is not suspected as being the cause of the abdominal pain. A typical patient with such a condition is an emaciated woman between the ages of sixty and eighty.

Retroperitoneal hemorrhage resulting from trauma may produce severe abdominal pain, and clinically an associated paralytic ileus may be present. The retroperitoneal hemorrhage may or may not be associated with rupture of the kidney. In reviewing the traumatic injuries at Bellevue Hospital on two occasions,[8, 9] I have been impressed by the number of patients who presented a typical picture of an acute surgical condition of the abdomen although the symptoms resulted from hemorrhage outside the peritoneal cavity associated with reflex ileus. This condition should be suspected if the injury has been over the lumbar region, and there may be evidence of abrasions, ecchymosis or swelling. Occasionally, there is an associated fracture of the transverse process of one of the lumbar vertebras. This history and physical findings are most important in the differential diagnosis in this condition. Plain films of the abdomen may be misleading, for they may indicate fluid levels and make one suspect a true organic obstruction, when in reality the cause is a functional disorder of the gastrointestinal tract that does not require laparotomy.

Summary

Acute abdominal pain can be more accurately interpreted by a carefully taken history and study of the physical findings than by any other means. The results of laboratory and x-ray studies are frequently misleading, and one should not place too great reliance upon them in evaluating the indications for laparotomy.

The consultant should be given the opportunity to obtain the history directly from the patient. Thus, he can better evaluate the symptoms since he is studying an individual patient and not a case report.

130 East 79th Street

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AN EPIDEMIOLOGIC STUDY OF INFECTIOUS MONONUCLEOSIS IN A NEW ENGLAND COLLEGE*

Alfred S. Evans, M.D.,† and Elizabeth D. Robinton‡

NEW HAVEN, CONNECTICUT, AND NORTHAMPTON, MASSACHUSETTS

THE frequency of epidemics of infectious mononucleosis in a community or in institutions is difficult to determine since this disease is not usually reported to public-health agencies. Yet if one takes the published literature as a sounding board for the behavior of this condition during the last twenty-five years in the United States, one is struck by the fact that despite an increasingly voluminous number of reports devoted to its clinical and laboratory aspects the number of publications dealing with actual epidemics of infectious mononucleosis is singularly few. For example, in the first three decades of this century and after West's report[1] of an outbreak in an Ohio community in 1896, many accounts appeared of similar epidemics occurring in mental institutions,[2] boarding schools,[3, 4] children's-hospital wards[5, 6] and the military camps of World War I.[7] Yet in more recent years such reports have been few indeed. Even in large colleges, where individual contact is close, spread from one person to another appears uncommon, and its occurrence in roommates is distinctly unusual.[8-10] Furthermore, cross infections on open hospital wards have been notably absent,[8, 11] and in the close confines of military ships during the last war evidence of contact spread was not seen.[12, 13]

This apparent change from an epidemic to a sporadic or endemic disease suggests either that the contagiousness of infectious mononucleosis as now encountered is low or that the disease may occur in such a mild form as to go unrecognized. Evidence on this latter point has been reported from recent studies in military camps both in this country[14] and in Scotland[15, 16] suggesting that for every clinically recognizable case there may be many others with subclinical or inapparent infections. It is thus conceivable that the present sporadic nature of infectious mononucleosis might be more apparent than real since these very mild cases might escape detection. An opportunity to investigate this problem further recently presented itself at Smith College, Northampton, Massachusetts, where the number of cases of infectious mononucleosis appeared to be increasing during the winter of 1948-1949 as compared to the incidence in previous years. The purpose of this paper is to present the results of a search for subclinical and inapparent infections in a dormitory unit of this college in which 5 clinical cases had occurred within a period of a month and, in addition, to consider the general epidemiology of infectious mononucleosis at this institution during the past four years.

Incidence

The number of cases diagnosed yearly as infectious mononucleosis at this college during the past four years as compared to similar figures for five other common infectious diseases is shown in Figure 1. It should be noted that the total college population has remained remarkably stable during this period. As evident from the graph, the incidence of infectious mononucleosis has shown a steady increase in the last four years, in contrast to the general downward trend of five other common illnesses. In 1948 to 1949 some increases can be seen for mumps and German measles, but the number of cases of

*From the Section of Preventive Medicine, Yale University School of Medicine, and the Department of Hygiene and Bacteriology, Smith College.

†Instructor in preventive medicine, Yale University School of Medicine; associate physician, Grace-New Haven Community Hospital; formerly, National Institutes of Health Postdoctorate Fellow.

‡Assistant professor of hygiene and bacteriology, Smith College.

infectious mononucleosis was nearly twice as great as in any of the preceding three years.

At Yale University a similar sharp upward rise was seen in 1946-1947 over the preceding ten years, and by 1948-1949 three times as many patients were hospitalized in the infirmary with this diagnosis as in any year prior to 1946. At Harvard University[9] and at Dartmouth College,[10] increases of this magnitude have not been observed, but there has been some upward tendency over a ten-year period. Infectious mononucleosis has been an important source of hospital admissions at these institutions during the ten-year period; at Dartmouth College it represented 0.74 per cent of total infirmary admissions,[10] at Harvard University, 1.5 per cent[9] and at Yale University, 1.7 per cent. At Smith College it accounted for 0.78 per cent of the admissions to Mason Infirmary in 1945-1946, and by 1948-1949 this had increased to 3.4 per cent.

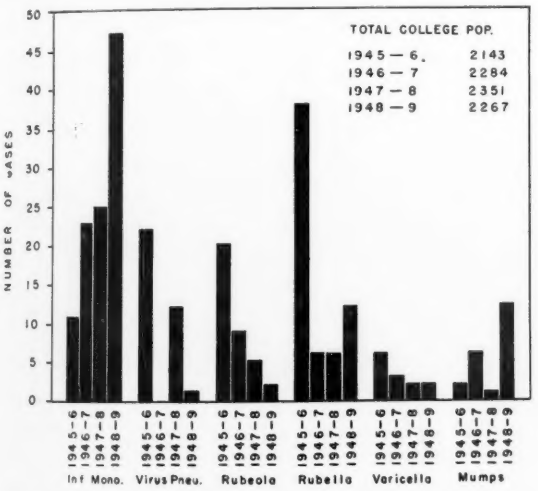

FIGURE 1. *Number of Cases of Infectious Mononucleosis as Compared to Five Other Common Infections at Smith College during the Period 1945 to 1949.*

Season

The incidence at Smith College month by month for the four-year period is presented in Figure 2. No general seasonal trend is apparent, which is in accord with the experience at other colleges,[9, 10, 17] as well as with that of the Army during the last war.[18] It is interesting to note, however, that the highest monthly peaks occurred in the months immediately following the end of the summer, Christmas or spring vacations.

Severity of the Disease

A rough estimate of the seriousness of an attack may be judged by the length of hospitalization. These figures (Table 1) appear reliable, since few patients were allowed to convalesce at home as is the practice at some institutions. It can be seen that there has been no significant increase in the severity of an attack on the basis of this criterion, the average duration ranging from nine to sixteen days over a four-year period.

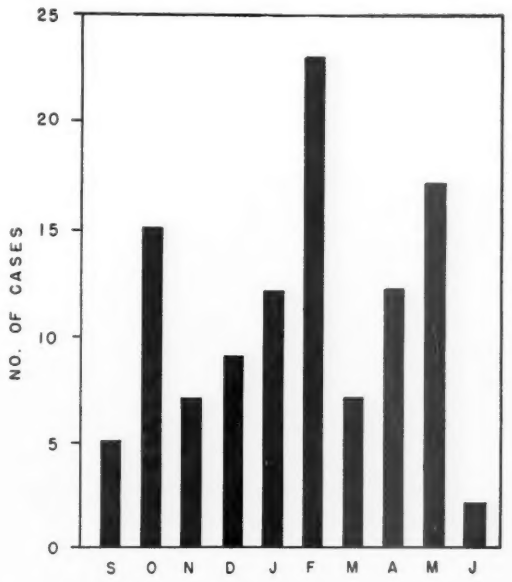

FIGURE 2. *Total Number of Cases of Infectious Mononucleosis by Months over a Four-Year Period.*

Diagnostic Criteria

In view of the increasing number of cases diagnosed as infectious mononucleosis, it is important to decide whether this represents an actual increase in the incidence of the disease or is merely a reflection of more frequent laboratory studies and perhaps less stringent diagnostic criteria. In a review of the hospital records on this point, it was found that all cases diagnosed during the past four years had a clinical course suggestive of infectious mononucleosis and a lymphocyte count over 45 per cent, pathologic forms invariably being seen. The emphasis laid on the necessity of an elevated heterophil-antibody agglutination titer as an integral part of the diagnostic triad has varied from year

TABLE 1. *Average Number of Days in Hospital (1945 to 1949).*

Year	No. of Cases	Days in Infirmary
1945-46	11	16.0
1946-47	24	9.4
1947-48	25	15.2
1948-49	47*	13.4

*Includes 3 probable cases.

to year (Table 2). The decline in the number of cases with an elevated titer during 1948-1949 suggests that a part at least of the increased number of patients admitted to the hospital with the diagnosis of infectious mononucleosis for this period is due to the willingness on the part of the physician to disregard the serologic aspects if the clinical and hematologic evidence is satisfactory. Similar tendencies were noted in the New Haven Hospital series covering the period from 1921 to 1946 in which only 60 per cent of the cases were serologically positive,[17] although higher percentages have been noted in similar age groups.[9, 10]

TABLE 2. *Percentage of Cases of Infectious Mononucleosis with Elevated Heterophil-Antibody Agglutination Titers (1945-1949).*

YEAR	NO. OF CASES TESTED	ELEVATION OF TITER
		%
1945-46	11	73
1946-47	19	74
1947-48	24	91
1948-49	47	60

HOME STATE OF PATIENTS

An analysis of 91 cases according to the state in which the student grew up revealed that 22 states were represented and that over half the patients came from Massachusetts, New York and Connecticut. Since students from these states constitute the dominant segment of the college population as a whole, it must be concluded that geographic origin in the United States played no demonstrable part in the susceptibility to this disease. In many of the Army reports during World War II, the widespread distribution of the home locale of the patients has been similarly noted.

INCIDENCE IN INDIVIDUAL DORMITORIES

The living facilities at Smith College are so arranged that groups of girls varying from 17 to 78 in number are housed in individual dormitories, of which there are 37. Each housing unit is provided with its own kitchen facilities and dining room. Daily contact at mealtime thus affords an opportunity for common exposure to infectious diseases within that unit. If infectious mononucleosis were a readily transmissible disease and the population were susceptible, it appears likely that from time to time certain housing units would have a high rate of incidence subsequent to the occurrence of the disease in one of its inhabitants. On scrutiny of the distribution of cases by dormitories both yearly and cumulatively for 1945 to 1949, no evidence of a preponderance of cases in a single unit was found. The total incidence for separate dormitories per hundred residents over the entire period varied from 0 to 14.8, and in the dormitories with the highest rates, the cases were spread over the four-year period. The location of the dormitories on the campus also appeared unrelated to the occurrence of infectious mononucleosis. The dormitory with the highest yearly rate had 6 cases among 75 girls during 1948 to 1949, occurring over a five-month period. In another dormitory, however, 5 cases were diagnosed within a period of one month. The apparent prevalence in this unit offered an opportunity to investigate the possibility of inapparent and subclinical cases occurring in the dormitory, and the results of this survey are presented below.

SURVEY IN A SINGLE DORMITORY

This dormitory consists of 3 housing units designated here as A, B and C. The units house 58 girls and 5 other personnel who all eat together and frequent a common lounge room.

The first case of infectious mononucleosis in this dormitory was diagnosed on January 13, 1949, and the second on January 26, and 3 additional patients were admitted to the infirmary during the month of February — 1 on the 7th, 1 on the 9th, and 1 on the 14th. All three housing units were represented. The environmental circumstances were such that ready transmission of a highly contagious disease to susceptible persons would be expected and might be evidenced by the occurrence of both clinical and subclinical cases. On this basis and with the knowledge that cervical adenopathy, pathologic lymphocytes and occasionally high heterophil-antibody titers may persist for several weeks after onset of symptoms, a survey of all 3 units, including house supervisors and kitchen personnel, was carried out on February 25.

The survey included the following procedures: a careful history for any illness within the past month, however minor, that might not have come to the attention of the college physician; palpation for enlargement of cervical lymph nodes, a simplified, qualitative test for heterophil-antibody determination[19] carried out so that it would be considered positive in all persons with an equivalent serum titer of 1:80 or over and a blood smear stained with Giemsa on which 100 cells were enumerated if the lymphocyte count were under 40 per cent and in which 200 cells were counted if the lymphocyte percentage were higher. It should be noted that particular care was taken in evaluating the type of lymphocytes encountered, and for this purpose they were placed in three categories: normal lymphocytes; "atypical" lymphocytes, in which were grouped cells that showed only one of several features of the infectious-mononucleosis cell such as peripheral basophilia, lobulated nucleus, foamy vacuolated cytoplasm or large size with fragile wall, but in which the cells were not believed to be unequivocally characteristic; and pathologic

lymphocytes, including only cells that were considered very characteristic of infectious mononucleosis. This was done because it was believed that individual interpretations of cell type varied widely and that often lymphocytes that would be considered normal under ordinary circumstances might be classified as the "infectious-mononucleosis type" if abnormalities were carefully searched for.

Personal histories of illness, records of the college physician and infirmary admissions within the preceding month were all analyzed for mild illnesses that might have represented undiagnosed infectious mononucleosis.

Fifty-six residents were surveyed on February 25, and the remaining 7, who were unable to be present on this occasion, were checked on March 1. The results of this survey are indicated in Table 3, which excludes the 5 patients with infectious mononucleosis who had recently returned from the infirmary. Three of the 58 residents had mononuclear counts (lymphocytes in addition to monocytes) of over 50 per cent, but in these cases no cervical adenopathy was found, no illness had been experienced in the last month and the heterophil-antibody test was negative. Furthermore, abnormal lymphocytes were present in only one blood smear, which showed a total lymphocyte count of 50 per cent including 1.5 per cent atypical cells and 0.5 per cent pathologic cells. It should also be noted that none of the 58 subjects examined showed over two atypical or one pathologic lymphocyte per 100 cells.

One student was found to have slightly enlarged cervical lymph nodes and a faintly positive heterophil-antibody test, but her blood smear was normal. She had experienced a head cold on February 5 but had had no other illness. One other girl had a faintly positive heterophil-antibody test but no other hematologic or clinical evidence of infectious mononucleosis. These 2 students are probably examples of a high normal (1:80) heterophil titer since the qualitative test employed was only faintly positive in both.

These 5 students just discussed and 11 others who had mononuclear counts over 40 per cent were reexamined on March 14. The clinical and hematologic results of this follow-up study were negative: no person showed evidence of infectious mononucleosis.

Histories or clinical records from 21 of the residents disclosed that they had suffered from illnesses other than infectious mononucleosis during the preceding month. These diseases included the following: 5 with sore throats, 4 with colds, 5 with some other type of upper respiratory infection, 3 with gastrointestinal disturbances, 2 with primary atypical pneumonia and 1 each with mumps and gingivitis. The blood counts of these residents, taken when they were ill or at the time of the survey, revealed no evidence suggesting that a diagnosis of infectious mononucleosis had been missed. Finally, no other case of the disease occurred in this dormitory during the rest of the college year.

It should be added that the 5 students who had recently recovered from infectious mononucleosis were included in the survey group to determine whether the residual findings would be sufficient to suggest the diagnosis. Four were found to have residual adenopathy, 2 had definite and one suggestive hematologic changes, and 1 had a positive heterophil-antibody test. Thus, a definite diagnosis could have been made on residual findings in 3, a probable diagnosis in 1 and no diagnosis in 1.

TABLE 3. *Results of Survey of 58 Residents in a Dormitory for Evidence of Subclinical Infectio with Infectious Mononucleosis.**

Survey No.	No. of Girls	Mononuclear Counts†			Enlarged Cervical Lymph Nodes	Positive Heterophil-Antibody Test
		Under 40%	40-49%	Over 50%		
1	1			+	0	0
2	1			+	0	0
3	1			+	0	0
6-23	18		+		0	0
24	1	+			+	+
25	1	+			0	+
24-58	35	+			0	0

*All abnormalities encountered are indicated by "+".
†Lymphocytes in addition to monocytes.

Occurrence in Roommates

It has already been pointed out that infectious mononucleosis rarely involves roommates. Thus, over a period of ten years no such case was noted at Dartmouth College,[10] at Harvard University[9] or at the University of Pennsylvania.[8] At Yale University, where one of us has inquired into the contact history of about 50 patients during the last two years, only 1 such occurrence has been found. Here, typical infectious mononucleosis developed in 2 of 4 roommates with an onset three days apart, Serologic and hematologic studies on the other 2 roommates, as well as on an intimate associate, revealed no inapparent or subclinical infection. From the standpoint of the susceptibility of the 2 students in whom the disease developed it is perhaps significant that they had been friends since childhood, had attended the same high school and had roomed together ever since entering Yale three years before. Thus, their exposure to infectious mononucleosis, or more properly their lack of exposure, may have been nearly identical. At Smith College during the present study 1 possible additional case was noted: 2 girls became ill within three days of one another, but only 1 presented a classic picture. In the other, although lymph-node enlargement including the liver and spleen occurred, neither a high lymphocyte count nor an elevated

heterophil-antibody titer developed. Patients like this one may present difficult diagnostic problems, and yet the case mentioned strongly suggests on epidemiologic grounds that cases of infectious mononucleosis may occur that present the clinical picture of the disease but fail to show the usual hematologic or serologic changes.

Occurrence in Lower as Opposed to Upper Classes

In Table 4 the distribution of patients according to the college class is shown. The tendency of the disease to be more frequent in freshmen and sophomores should be noted.

Table 4. *Cases of Infectious Mononucleosis According to Class in College.*

Year	Freshman Class	Sophomore Class	Junior Class	Senior Class	Graduate Students	Faculty
	No. of cases	No. of cases	No. of cases	No. of cases	No. of cases	No. of cases
1945-46	2	5	0	4	0	0
1946-47	4	12	8	0	0	0
1947-48	8	9	5	3	0	0
1948-49	20	12	9	4	1	1
Totals	34	38	22	11	1	1

Discussion

Over a four-year period the frequency of infectious mononucleosis at Smith College, Northampton, Massachusetts, has been found to be increasing, in contrast to the general downward trend of five other common infectious diseases. Part of this apparent increase may have been due to an increased willingness on the part of the physician to make this diagnosis in the absence of an elevated heterophil-antibody titer. The occurrence of this condition did not seem to be related to the season of the year, the home state of the patient or the dormitory in which she lived. It appeared to be more frequent, however, in freshmen and sophomores than in juniors and seniors. The disease was noted only once in roommates.

A survey of a dormitory of 63 residents in which 5 cases of infectious mononucleosis had occurred within a period of a month was carried out in a search for the presence of subclinical or inapparent infections. No evidence that any of these subjects had mild or unrecognized infectious mononucleosis was found. This observation is at some variance with the results of similar studies carried out in Army camps and hospitals during the last war.[14-16] The reasons for this are not clear. It is possible that strain variations in the hypothetical causative agent influence its epidemicity.

The concept that infectious mononucleosis under most circumstances is now a sporadic and endemic disease and has a low contagiousness appears to fit best with available evidence. The difficulty in transmitting it experimentally to human volunteers is consonant with this idea.[20, 21] It is not possible to decide whether this circumstance is due to immunity acquired through a mild and unrecognized infection early in childhood or to other factors such as low virulence of the causative agent.

Summary

An epidemiologic study of infectious mononucleosis at Smith College over a four-year period is presented.

A survey of a dormitory of 63 residents in which 5 cases of infectious mononucleosis had occurred within a period of a month failed to demonstrate evidence of inapparent or subclinical infections in others of this group.

Infectious mononucleosis now appears under most circumstances to be a sporadic disease of low contagiousness.

We are indebted to Dr. Marion F. Booth, college physician, Smith College, and to Miss Dorothy Huey, director, Smith College Infirmary, for their co-operation and suggestions in this study, and to Miss Mary George Antonak for technical assistance.

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THE INCIDENCE OF SWOLLEN ARMS AFTER RADICAL MASTECTOMY AND SUGGESTIONS FOR PREVENTION*

ERNEST M. DALAND, M.D.†

BOSTON

ON a number of occasions when a patient has been told that she would have to have her breast removed she has asked if that meant loss of use of her arm. There have been enough cases in the community in which postoperative swelling of the arm has interfered with or destroyed the function of the arm for this fear to be constantly found among women. Stewart and Treves[1] state "conservatively speaking, some degree of swollen arm supervenes after radical mastectomy in about 70 per cent of women." Macdonald[2] says "after radical mastectomy, 40 to 50 per cent of women have moderate or severe lymphedema, not due to recurrent disease" and advocates removal of a segment of the axillary vein to prevent it.

All surgeons have seen this complication, but we have been impressed by its rarity in the Pondville Hospital clinics. In view of such widely quoted statements as those mentioned above it seemed desirable to examine a group of patients at various periods after operation to see whether our impressions were correct or erroneous. After the results of these studies have been presented the measures that are used to avoid the development of swollen arms will be discussed. Much has been written about the treatment of this situation, but the results are poor after swelling has occurred. Prevention is a better measure.

This study is not concerned with the swollen arms of patients with known recurrent cancer of the breast, but only with the swelling that is presumably due to the treatment carried out. Ninety patients who have had radical mastectomies, all but 1 for cancer, have been examined. Fifty of these were consecutive cases seen in private practice in which the patients reported for follow-up study from two and a half months to twenty-five years after operation. Thirty-nine were consecutive cases examined by me in the Pondville Hospital follow-up clinic. Some of the operations had been performed by members of the visiting staff, and many by residents in surgery. Two patients who had radical procedures secondary to operations elsewhere are included. One woman had a radical mastectomy after a frozen-section examination but was later found not to have had cancer. All patients were apparently free of disease at the time of the examination.

It is probable that there is a certain variation in the size of the arms in normal women, owing partly to whether they are left-handed or right-handed. For the purposes of this study it was supposed that the arms were of equal circumference before operation. The greatest circumference of the upper arm on each side was determined, and this reading was not made at a constant distance from the shoulder. Usually, the greatest circumference on the operated side was 1 or 2 cm. lower than that on the normal side. This seemed to be due to a relaxing of the structures of the upper arm from the dissection of the axilla and the removal of the pectoral muscles. We have not taken into account, in the tables presented below, the size of the patient or her arms. Obviously, swelling of 1 cm. is of more importance in a thin arm than in a fat one.

The axillary lymph nodes were involved in 51 cases in this series. No nodes were found in 38, and no cancer was present in 1 operated case. No relation between the presence of lymph-node metastasis and swelling of the arm was found.

Halsted,[3] in 1921, reported from his studies that "although blocking of the lymphatics and occasionally also of the veins was the underlying factor, infection played a conspicuous part in the determination of the amount of swelling and the time of its manifestation."

Veal[4] points out that there are three types of edema — lymphatic, venous and a combination of the two. He had included the cases with recurrent cancer in his study and made the following observation:

> Edema resulting from obstruction of the axillary and subclavian veins is by far the most common cause of swelling of the arm following operation. The most frequent cause of the venous obstruction is recurrence of the malignancy along the course of the veins. In some cases the venous occlusion results from benign scar formation. . . . Lymphatic stasis is a secondary result of the venous obstruction and if prolonged will lead to permanent blockage of the lymphatic flow. Infection is prone to develop and may lead to further obstruction and cause a greater degree of swelling.

Devenish and Jessop[5] believe that postoperative swelling is due to lymphatic obstruction and that the rise in venous pressure occurring during exercise is a factor in edema formation after lymphatic obstruction has occurred. They state that postoperative swelling occurs in 1 of 6 cases.

RESULTS OF MEASUREMENTS

In 5 patients the circumference of the upper arm on the operated side was less than that of the nor-

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From the Pondville Hospital (Massachusetts Department of Public Health), P. O. Walpole, Massachusetts.
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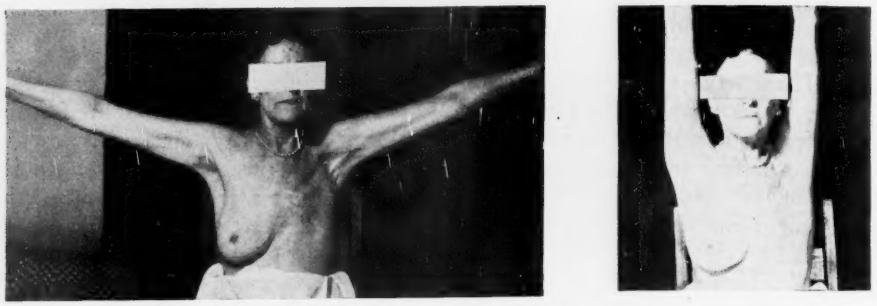
†Instructor in surgery, Harvard Medical School; visiting surgeon, Massachusetts General Hospital; chief of staff, Pondville Hospital.

mal. Measurements of the forearm showed this to be true in 6 cases. This could be explained on the basis of atrophy of the arm, but in each case the patient had normal function and no evidence of muscle atrophy. It is better explained by the normal variation between the two arms and the inaccuracy of the measurements.

There were 13 patients who showed no difference in the measurements of the two arms (Table 1). Twenty-one had no swelling of the upper arm, and 31 none in the forearms. An increase of 0.5 cm. in circumference was noted in 15 upper arms and 13 forearms. This was considered within normal limits, since it represents a change in diameter of only 0.15 cm. There were then 41 patients (45 per cent) with no swelling of the upper arm and 50 patients (55 per cent) with none of the forearm. A typical patient in this group is shown in Figure 1.

Anything over 0.5-cm. increase in circumference has been considered "swelling." Increases of 1 cm. to 2.5 cm. have been considered as "slight swelling." There were 28 upper arms and 25 forearms. None of these had brawny lymphedema, and most of the upper-arm swellings were soft because of relaxation from the axillary dissection. All these patients had normal use of their arms, and many were not aware that they had any swelling. Slight swelling occurred in 31 per cent of upper arms and 27 per cent forearms. Typical patients are shown in Figures 2 and 3.

"Moderate swelling" was the classification when the arms showed an increase of 2.5 to 4.5 cm. in size.



A B

FIGURE 1. *Patient Five Years after Radical Mastectomy for Cancer, Showing No Disability or Swelling of the Arms.*

TABLE 1. *Arm Measurements (Circumference) after Radical Mastectomy.*

MEASUREMENT	UPPER ARM NO. OF CASES		FOREARM NO. OF CASES	
No swelling:				
Decrease in size	5		6	
No change from normal arm	21	(45.0%)	31	(55.0%)
Increase of 0.5 cm.	15		13	
Slight swelling:				
1.0 cm.	8		10	
1.5 cm.	16	(31.0%)	10	(27.0%)
2.0 cm.	4		5	
Moderate swelling:				
2.5 cm.	8		3	
3.0 cm.	3		2	
3.5 cm.	2	(17.0%)	1	(10.0%)
4.0 cm.	3		1	
4.5 cm.	0		2	
Severe swelling:				
5.0 cm.	0		2	
6.0 cm.	2		0	
7.0 cm.	2	(5.5%)	2	(6.6%)
10.0 cm.			1	
11.0 cm.			1	
15.0 cm.	1		—	
Totals	90		90	

FIGURE 2. *Patient Three Years after Radical Mastectomy. There is a 1-cm. enlargement of the left arm, but no disability.*

In this group there were 16 upper arms (17 per cent) and 9 forearms (10 per cent). In only 1 case was there any limitation of motion, and that was very slight. In some cases the edema was firm and seemed to be of the lymphatic type. Aside from difficulty in obtaining sleeves to fit the enlarged arm the patients had few complaints. A typical patient is shown in Figure 4.

"Severe swelling" of the upper arm was present in 5 patients (5.5 per cent), and severe swelling of the forearm in 6 (6.6 per cent). Many of these had severe disability from the weight of the arm, although all but 2 had normal range of motion. The

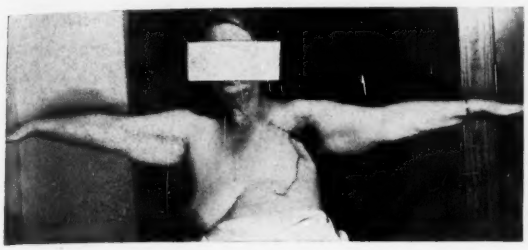


FIGURE 3. *Patient Two and a Half Months after Radical Mastectomy.*

reasons for the swelling in these cases is discussed below. A typical patient is shown in Figure 5.

In 2 cases the operations were performed by Dr. Robert Greenough, who first described the technic used. I assisted in the operation on 1 patient twenty-five years ago. She has never had any swelling of the arm or any disability. The other patient was examined twenty-two years after operation. She showed 0.5-cm. swelling of the upper arm and 1.5-cm. enlargement of the forearm, but she thought this was due to a fracture of the surgical neck of the humerus six months previously.

METHODS OF PREVENTION

The Greenough modification of the Rodman incision[6] (Fig. 6) was used on all patients in the group studied. This consists of a transverse axillary incision, with an arrow-head-shaped incision about the breast. A segment of skin between the breast and the axilla is removed. The axillary dissection is completed before the breast is removed. When the incision is closed there is no scar on the arm.

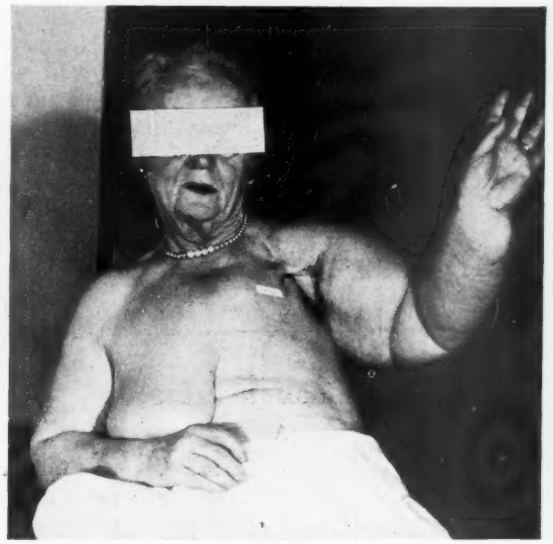


FIGURE 4. *Patient Four Years and Three Months after Radical Mastectomy.*
There had been sloughing of the skin flap, a large amount of serum and moderate sepsis. The arm is badly swollen; function is fair.

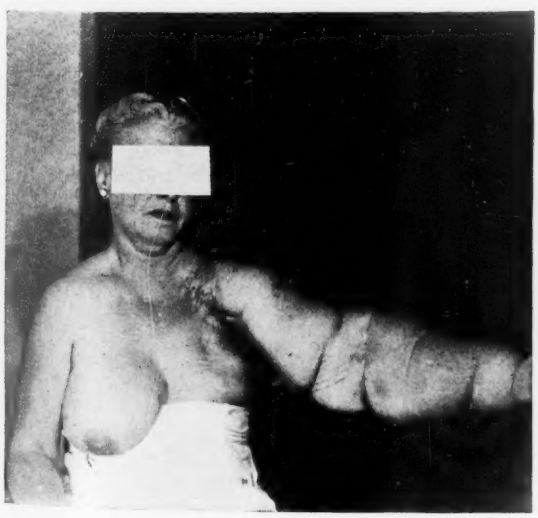


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FIGURE 5. *Patient Five Years after Radical Mastectomy (Axillary Lymph Nodes Were Involved).*
This patient received large amounts of x-ray therapy through two fields. There was no sepsis. The upper arm is enlarged 15 cm., and the forearm 11 cm. Function is still fair.

Nonabsorbable ligatures of silk or, in later years, cotton are used. We prefer to drain all the wounds and to have the drains in place three to five days.

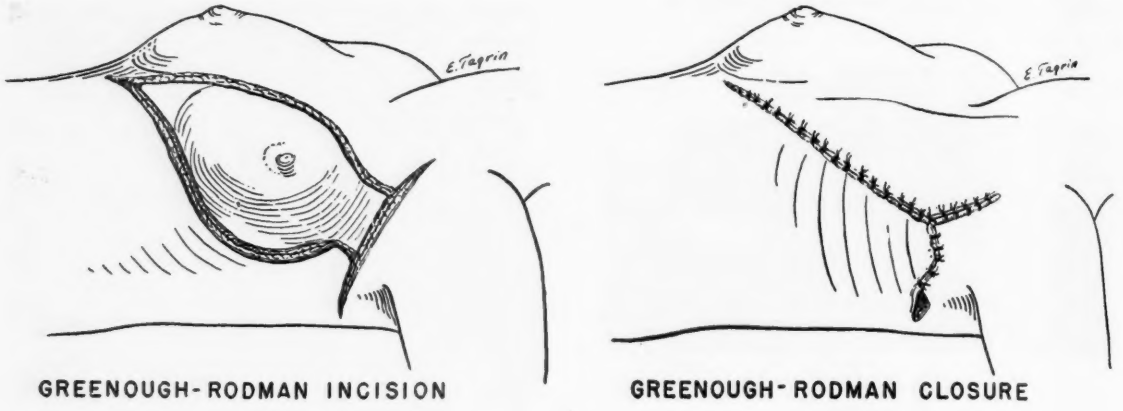

FIGURE 6. *Greenough Modification of the Rodman Incision. No part of the incision lies on the arm.*

We see no objection to drainage, but it has a distinct advantage. We had previously noted very severe complications from extensive hematomas in undrained mastectomy wounds. Pressure to a moderate degree is applied to a large dressing.

Early use of the arm is the rule. It has been our practice for many years to use a tight chest binder to hold the dressing in place. A second binder is folded lengthwise three times; it is then used as a shoulder strap to hold the first binder firmly in place. It is fastened to the back of the binder, laid over the shoulder, fastened to the front of the binder and then brought over to make a sling for the upper arm[7] (Fig. 7). The lower arm is left free. The purpose of the sling on the upper arm is to prevent much adduction but it does support the arm from the bed, and it allows the patient to use the forearm without pain. It is not uncommon to see a patient feeding herself with the arm of the operated

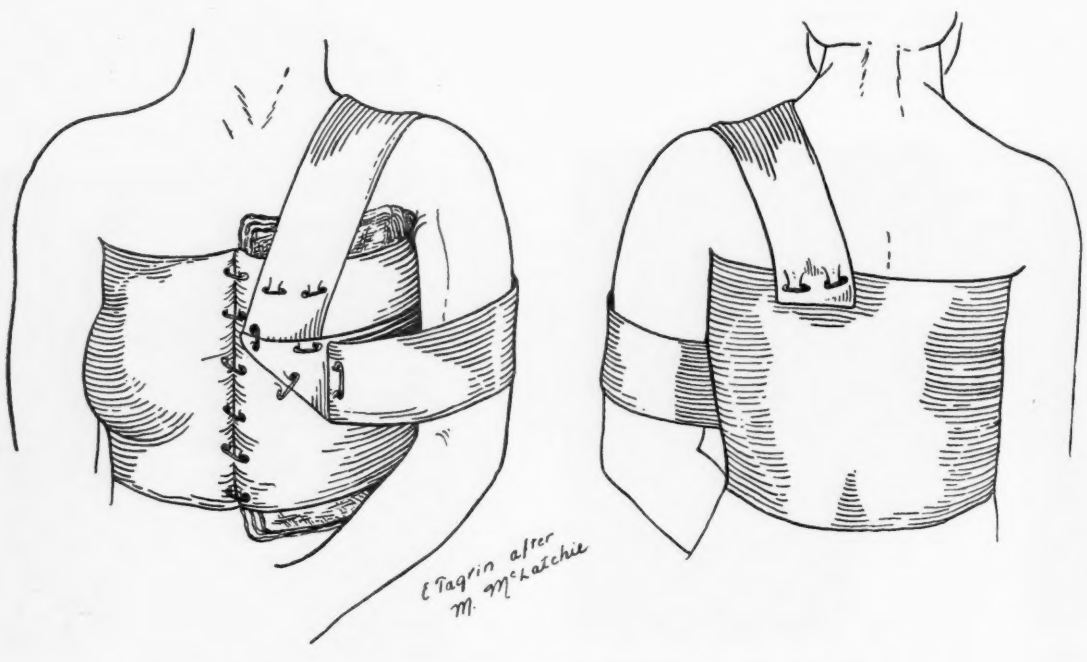

FIGURE 7. *Breast Binder to Restrict Abduction, but Allow Full Use of the Arm Otherwise.*

side the day after operation. The restricting sling is removed at the time of the first dressing, usually on the third postoperative day.

The patient is allowed to use the arm at will but is not told to do exercises. We believe it is important that the patient's attention should not be drawn too much to the arm or to the possibility of getting a stiff arm. By gradually making it possible for her to use it and occasionally asking her to show what she can do with it, one accomplishes this aim. The surgeon should adopt the attitude that he expects the patient to use it as well as before. Patients invariably are able to comb their hair within two weeks, and many at the end of a week.

We regard it as a mistake to fasten the whole arm down to the chest and keep it there for many days, as advocated by some surgeons. Often the excuse for doing this is the fact that the wounds are undrained and excessive fixation is necessary. Such a period of disuse encourages stiffness and requires heroic efforts to get the function back. In a few cases in which full function has not been obtained it has been due to the patient's unwillingness to use her arm early, and sometimes her apprehension has been due to the knowledge that another patient never did use her arm again. To the argument that early use of the arm increases the flow of lymph our answer is that drainage will care for the lymph and that function is all important.

X-Ray Therapy

It has not been our policy in recent years to use preoperative x-ray treatment. We have not given postoperative treatment routinely and at present do not use it unless disease has been left at operation. Thirteen patients in this series did receive prophylactic treatment although it was believed that all disease had been removed. It is noteworthy that 9 of these patients had edema of the upper arm with enlargement of 2.5 cm. or more (2.5, 3.0, 3.5, 3.5, 4.0, 6.0, 7.0, 7.0 and 15.0 cm.). Six had more than 2.5-cm. enlargement of the forearm — 2.5, 3.0, 4.0, 4.5, 7.0 and 11.0 cm. (Table 2).

The patients experiencing the greatest amount of swelling were those who received the highest dosages of x-rays. In 1 case of moderate swelling a moderate infection of the wound was also noted. It seems fairly certain that x-ray treatment was a factor in causing the swelling of these arms. It might be more accurate to say that operative treatment in addition to x-ray therapy was a factor.

Sepsis

Sepsis was present in rather severe degree in 3 cases, and a massive hematoma in 1. In 2 of the cases of sepsis severe swelling developed (Table 2).

Other Results

Holman, McSwain and Beal[8] have made a study similar to the present one. They found no swelling (not more than 1-cm. change) in 28 per cent, up to 3 cm. in 25 per cent, 3 to 6 cm. in 37 per cent and over 6 cm. in 9 per cent. More cases of severe swelling occurred among patients who had received irradiation.

Nicholson and Grady[9] examined 230 cases after radical mastectomy and reported no swelling in 56 per cent, slight in 23 per cent, moderate in 14 per cent and severe in 7 per cent.

Treves[10] believes that swelling of some degree occurs in 25 per cent of operated cases.

Guthrie and Gagnon[11] have made a very careful summary of the subject and state that prevention of edema is carried out by "placing the incision off the arm; a sharp anatomic dissection of the axillary contents; the use of very fine nonabsorbable sutures (we prefer size No. 80 cotton); no drainage; pressure dressing; early mobilization of the arm; and avoidance of infection."

Table 2. *Relation of X-Ray Therapy and Sepsis to Postoperative Swelling.*

Enlargement	Upper Arm			Forearm		
	No. of cases	X-ray therapy	Sepsis	No. of cases	X-ray therapy	Sepsis
cm.						
Moderate swelling:						
2.5	8	(1)		3	(1)	
3.0	3	(1)	(1)	2	(1)	
3.5	2	(1)	(1)	1		
4.0	3	(1)		1	(1)	
4.5	0			2	(1)	
Severe swelling:						
5.0	0			2		(1*)
6.0	2	(1)	(1)			
7.0	2	(2)		2	(1)	
10.0				1		
11.0				1	(1)	
15.0	1	(1)				

*Hematoma.

Conclusions

An analysis of 90 cases of cancer of the breast after radical mastectomy convinces us that the regime used in the Pondville Hospital clinic is satisfactory.

Sepsis must, of course, be avoided, for the results are long lasting.

We agree with Guthrie and Gagnon that the incision should be kept off the arm, and we prefer the Greenough modification of the Rodman incision, a minor change from their technic.

One should avoid the accumulation of serum in the wound — whether by drainage or not is the concern of each surgeon. Serum left in the wound causes fibrosis.

There must be a good reason for giving x-ray therapy after operation. We have not found that such therapy avoids recurrence, and we prefer to save it for the treatment of such recurrences if they occur. If it is given, it must be so administered that

there will not be a cicatricial band of scar through the axilla, for that will produce a swollen arm.

Early motion is most essential.

If these precautions are carried out there will not be many cases in which measurable swelling occurs.

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PROGRESS IN THE CLINICAL USE OF 3-(ORTHO-TOLOXY)-1, 2-PROPANEDIOL (MEPHENESIN) IN NEUROLOGIC DISORDERS*

Donald S. Bickers, M.D.,† George A. Cohn, M.D.,‡ and Margaret B. Rheinberger, Ph.D.§

CHICAGO AND NEW YORK CITY

THE distress of many motor disorders is produced by exaggerated stretch reflexes (spasticity), excessive resistance to passive movement (rigidity) or abnormal involuntary movement of central origin (hyperkinesia).

To be satisfactory, a therapeutic agent must be easy to administer, preferably orally, effective in prolonged administration and devoid of untoward side effects. Specifically, it should depress abnormal motor activity without impairing consciousness, coordination or normal motor functions. Numerous agents used on this service and elsewhere have failed in one or more respects. Parpanit,[1] Prostigmine and intravenous injection of procaine have been ineffective. Though the belladonna alkaloids have been helpful in selected cases (primarily in Parkinsonism), unpleasant side actions are frequently encountered in the gaining of a therapeutic effect. The ineffectiveness of aqueous and oil preparations of curare has been reported elsewhere[2] and confirmed by independent studies with curare in oil on this service.[3] The reported pharmacologic and clinical properties of Mephenesin (Myanesin) prompted our studies.

In 1946 Berger and Bradley[4] reported the first account of the properties of Mephenesin (3-orthotoloxy-1, 2-propanediol). In their study of the effect on animals of a large number of related compounds (alpha-substituted ethers of glycerol) this drug was chosen as the safest and most potent muscle relaxant. They attributed this action to spinal-cord depression in the absence of narcosis or evidence of peripheral-nerve, myoneural-junction or direct muscular-depressant action. The failure of Mephenesin to influence myoneural conduction was pointed out as a characteristic distinct from the mode of action of curare. The ability of the compound to antagonize strychnine-induced convulsions and its failure to influence Metrazol-induced convulsions except in paralyzing doses were cited as further evidence of a depressant action on the spinal cord. A synergistic action with barbiturates in anesthesia was postulated. This prompted their suggestion of clinical use in the form of an adjunct in anesthesia. In subsequent communications, Berger[5-7] and Berger and Bradley[8, 9] elaborated on the pharmacologic properties of the compound. No untoward side effects were observed in concentrations sufficient to produce muscle relaxation. The wide margin of safety between effective and lethal doses (by respiratory paralysis and cardiovascular depression) was further incentive for proposing clinical trial in spastic and hyperkinetic disorders. Other pharmacologic reports[10-12, 14-22] have yielded additional information through studies on small animals. These studies generally corroborate the initial reports on the low toxicity and wide effective range of Mephenesin. The transient action following intravenous injection has been correlated with a rapid fall in plasma concentration of the drug.[17, 18, 22] The metabolism has been partially determined[15] but is not yet fully understood.

The first clinical trial of the drug was reported favorably in 1947 by Mallinson,[23] who used it as an adjunct in anesthesia without complication. A large number of reports have appeared since that time on its use in anesthesia,[12-14, 24-34] all of which, with one exception,[24] were based on an intravenously administered 10 per cent solution of Mephenesin in propylene glycol and alcohol. Though the drug was generally found to be effective as a muscle relaxant, complications such as thrombophlebitis, hemoglobinuria, hematuria and occasional deaths

*From the Neurological Service, Montefiore Hospital.

†Research associate in neurophysiology, Department of Psychiatry, University of Illinois College of Medicine, Chicago; formerly, assistant resident physician in neurology, Montefiore Hospital.

‡Member, Department of Surgery, Yale University School of Medicine; formerly, fellow in neurology, Columbia University College of Physicians and Surgeons, and assistant resident physician in neurology, Montefiore Hospital.

§Research associate in neurology, Columbia University College of Physicians and Surgeons; formerly, electroencephalographer, Montefiore Hospital.

from renal failure were noted. Its purported advantages over curare are disputed. It is apparent that the status of Mephenesin in anesthesia is as yet unsettled.

Reports dealing with the clinical use of Mephenesin in neurologic disorders have been less numerous. Stephen and Chandy[35] treated 12 neurologic patients with a 10 per cent solution of Mephenesin in alcohol and propylene glycol, and obtained transient improvement in most cases. They cited experimental evidence and the lack of electroencephalographic changes as the basis for their conclusion that the drug acts on the basal ganglions and brain stem. Hemolysis and hemoglobinuria occurred in 10 patients. Brooks et al.[36] similarly treated 2 patients with acute muscle spasm of poliomyelitis, without beneficial effect. Toxic symptoms in the form of flushing and blurring of vision appeared. Torrens and his associates[37] successfully treated the severe muscle spasm of a patient with tetanus by means of repeated intravenous injections of 10 per cent Mephenesin in propylene glycol and alcohol. Hunter and Waterfall[38] were able to control seizures of diverse origin for a brief time by a similar intravenously administered solution of the drug. They held the site of action to be the basal ganglions and brain stem, and suggested a trial in status epilepticus. In an effort to avoid complications attending the use of the 10 per cent solution, Schlesinger and his co-workers[39, 40] employed a 2 per cent solution of Mephenesin in physiologic saline solution intravenously in a variety of neurologic disorders, with transient improvement in some cases. No complications were encountered, and oral dosage was said to be ineffective. Berger and Schwartz[41] reported spectacular results with a 3.3 per cent aqueous solution administered orally to patients with chronic neurologic disorders. Gammon and Churchill,[42] using 1 or 2 per cent solutions intravenously, obtained results similar to those of previous investigators. No electroencephalographic changes were noted except in 6 patients with petit-mal epilepsy who evidenced diminution of percentage time spike and slow wave discharges. Oral dosage of 2 to 20 gm. per day resulted in severe leukopenias.[43] Three psychotic patients were improved. The effect of Mephenesin in psychiatric disorders has only recently been tentatively explored by others.[44, 45]

Generally, clinical reports have been uncontrolled and conflicting.

Material

Thirty patients were chosen as subjects from 120 on the Neurological Service of Montefiore Hospital. The diagnoses represented were: Parkinsonism, 6; Huntington's chorea, 5; dystonia musculorum deformans, 5; multiple sclerosis, 4; myoclonus epilepsy, 3; double athetosis, 2; myelitis and myelopathy, 2; syringomyelia and syringobulbia, 1; heredodegenerative disease of the central nervous system, 1; and Wilson's disease, 1. Since treatment was symptomatic, selection of cases was based on symptomatology rather than diagnosis, and patients with most severe symptoms were chosen provided the disability did not prohibit performance tests and the mental deterioration was not of such degree as to invalidate subjective reports. The average age for the series was forty and seven-tenths years; the average duration of illness was thirteen and four-tenths years.

The patients were divided into four approximately equal groups. Each group contained both control and treated subjects. Treatment periods of the groups were staggered over a period of four months to permit intensive study. No attempt was made to isolate patients under treatment from each other or from other patients. The treated patients were given 5 gm. of Mephenesin* daily for five weeks, and this dosage was kept constant throughout the series. Capsules were employed as the dosage form (0.25 gm. in a "000" plain gelatin capsule), and four capsules (1 gm.) were given at three-hour intervals (five times daily) from 9:00 a.m. to 9:00 p.m. We prepared identical placebo capsules for the control groups by tinting calcium lactate with cocoa to match the slightly grayish Mephenesin powder. All capsules, whether drug or placebo, were kept in individually labeled dark bottles whence doses were administered by the nurse, who then charted the dose.

One of us (D. S. B.) acted as observer of the first and third groups, and another (G. A. C.) of the second and fourth. The observer did not know which patients received placebo and which Mephenesin. Clinical observations were made daily by the physician and the charge nurse, who, on completion of therapy, submitted a written opinion of the nature of the medication given each patient.

Complete blood counts, urinalyses, fasting blood sugar and blood urinary nitrogen determinations were done on the entire series before medication was started. Blood counts and urinalyses (catheterized specimens in females) were performed twice weekly, fasting blood sugar and blood urinary nitrogen determinations were performed weekly, and all studies were repeated two weeks after completion of therapy. Electrical studies consisted of electroencephalograms (EEG) recorded simultaneously with electromyographic (EMG) tracings from the left extremities. Sample tracings were taken at irregular intervals during at least a three-hour period unless the patient slept in a shorter time or became very unco-operative. Patients were on stretchers, and there was every effort to make them comfortable before and during the procedure. Recordings were made in the evening in a quiet (street and building noises were not completely

*"Tolserol," kindly supplied by E. R. Squibb and Sons, New York City.

eliminated), dark atmosphere to encourage comparable states of relaxation and, if possible, sleep.

Two weeks after completion of all oral studies the drug was administered intravenously to 6 of the original 30 patients. Selection of the cases was made without knowledge of previous medication and was based on complete lack of response in all but 2 patients. Diagnoses were dystonia musculorum deformans (kinetic form), syringomyelia and syringobulbia, multiple sclerosis, post-encephalitic Parkinsonism, double athetosis and incomplete post-traumatic transverse myelitis. One patient, a four-and-a-half-year-old child with severe head injury, was studied at a later date, to observe the effect of the drug on true decorticate rigidity.*

A 2 per cent solution of Mephenesin in physiologic saline solution was prepared by heating of the solvent since the water solubility of the drug is 1.09 gm. per 100 cc. at 22°C. The supersaturated solution formed in cooling could then be autoclaved without deleterious effect. No precipitation was encountered either when the solution was used at room temperature or when it was warmed to body temperature.

Electrical technics were identical with those of the oral studies, except that tests were done in the afternoon, no attempt was made to obtain sleep, and continuous tracings were taken throughout the infusion and for fifteen minutes thereafter. The infusion was started at the rate of 40 drops per minute. After a short interval the rate was increased to 80 drops per minute. The infusion was continued in all cases until vertical nystagmus appeared. Dosage required for this effect ranged from 24 to 67 mg. per kilogram of body weight. Earlier reports described a fairly constant progression of toxic signs and symptoms with increasing dose so that larger doses, although possibly safe, are clinically useless. Clinical observation was continuous with frequent determinations of the neurologic status. Observation was continued until the patients had returned to pretreatment clinical status — usually for less than an hour. Blood samples were taken during and after infusion to detect possible hemolysis. Urinalyses were performed immediately and on two twenty-four-hour specimens after infusion.

Results

In the orally treated series, there was subjective and objective improvement in 6 patients. Five of these were in the treated group (myoclonus epilepsy, 2 and Huntington's chorea, heredodegenerative disease of the central nervous system and multiple sclerosis, 1 each); 1 patient (with multiple sclerosis) was in the control group. There was only subjective improvement in 4 patients; all were in the control group. Three of these were mentally deteriorated, and 2 markedly so. One patient (with double athetosis) was made markedly worse. "Toxic symptoms" were present in 10 patients — 4 in the treated group, and 6 in the control group. These consisted of flushing of the face (6 cases), nausea (3 cases), dizziness (3 cases), vomiting (2 cases) and urinary urgency, weakness, generalized pruritus, anorexia, tinnitus and weight loss (1 case each). The types and severity of toxic symptoms were similar in the treated and in the control groups. No symptom was of clinical significance except in 3 patients, all in the treated group. In the first, sweating was so profuse as to cause continual distress and led him to request his old medication. In the second, severe weakness caused frequent falls. In the third, anorexia and progressive weight loss were followed by severe nausea with hematemesis on the seventeenth day. Medication was stopped forthwith, and vomiting ceased. Melena cleared in the following week, but the source of bleeding was not determined before behavior problems necessitated the patient's transfer to a psychiatric institution. The possibility of tuberculous enteritis could not be excluded, and the symptoms could not definitely be attributed to Mephenesin.

Tolerance developed in only 1 patient. In this case peak effectiveness was reached by the end of the second day, remained unchanged to the fourteenth day and steadily decreased. All other clinical responses, both favorable and adverse, were constant throughout the test period.

The predominance of objective improvement, though small, lay in the treated group (5 cases, as compared with 1 in the control group). Subjective reports of improvement predominated in the control group. Consistent improvement was seen only in myoclonus epilepsy. The objective improvement seen in 1 patient in the control group led to the only error in estimation of therapy that occurred in patients showing objective improvement.

The results of intravenous administration varied widely. Five patients were improved; 1 patient with double athetosis and 1 with dystonia musculorum deformans were made worse by increased movements and ataxia, respectively. Improvement was characterized by progressive diminution of rigidity and resultant pain, accompanied by a pleasant sensation of warmth and relaxation. Spasticity was either undiminished or moderately increased; in no case was there any evidence of weakness. There was no sensory impairment. Toxic symptoms appeared in all cases. The usual order of appearance of toxic signs and symptoms was warmth and flushing of the face spreading later to the neck, shoulders and upper trunk, scleral injection and horizontal and vertical nystagmus. Four patients became drowsy, and 2 of the other 3 became dizzy; in the fourth patient neither drowsi-

*We are indebted to Dr. Charles E. Dowman, Jr., for the opportunity to study this case on the Neurosurgical Service of the Crawford W. Long Memorial Hospital, Atlanta. The technic was identical except that no electrical records were made, and serial blood samples were taken for plasma-level determinations. The determinations were performed through the courtesy of Dr. Arthur P. Richardson, of the Department of Pharmacology, Emory University School of Medicine.

ness nor dizziness occurred. Three complained of itching in the area of flushing. Three felt much relaxed subjectively. Weeping was present in 2. One patient complained of some respiratory distress and dryness of the mouth. Toxic symptoms usually increased with the dose. The duration of demonstrable clinical effect after infusion varied from fifteen to sixty minutes. Plasma-level determinations on the patient with decorticate rigidity secondary to head injury were as follows: control, 0; forty-one minutes (that is, end of infusion), 187.5 gamma per cubic centimeter; five minutes after infusion, 58.5 gamma per cubic centimeter; fifteen minutes after infusion, 45 gamma per cubic centimeter; and twenty-five minutes after infusion, 39 gamma per cubic centimeter. The peak blood level reached was approximately four and a half times the minimum level (40 gamma per cubic centimeter) said by Richardson[46] to produce mild toxic symptoms in adults.

The EEG's remained the same throughout the four examinations both for the controls and for those who received the drug by mouth. There were no significant differences between the two groups in pattern changes with drowsiness and sleep. Comparison of the EMG's of the control tests with those obtained while the patient was receiving medication showed an essentially similar character, magnitude and distribution of muscular activity recorded for comparable physiologic states. Five of the patients receiving placebos and 4 of those receiving Mephenesin had somewhat less EMG activity in the waking state during one or both of the examinations during medication. Since 3 of these slept only while they were receiving Mephenesin the reduction in waking EMG activity suggested some relaxation attributable to the drug. The EEG and EMG findings obtained during intravenous infusions generally paralleled the clinical changes. In patients who were clinically improved, 3 relaxed toward drowsiness and had accompanying EEG slowing and decreased EMG activity. The fourth showed no electrical evidence of muscular relaxation until fifteen minutes after the infusion was stopped. In 2 patients spontaneous ankle clonus developed, accompanied by EMG discharges in the rhythm of the clonus. These discharges resembled clonic bursts, which had occurred in their four previous records before, during and after oral administration of Mephenesin. One of the 2 patients made worse was disturbed by itching of the face and showed concurrent EEG changes to a less relaxed pattern and EMG evidence of increased activity as clinically apparent movements increased. The other was not disturbed initially by the procedure and experienced a period of subjective relaxation that was reflected in EEG and EMG findings.

Discussion

In a previous communication[2] the formidable difficulties encountered in the evaluation of spasticity due to spinal-cord injuries was discussed. The same difficulties obtain to even greater degree in measurement of the extent of and alterations in rigidity, hyperkinesia and spasticity caused by lesions other than transverse myelitis. The greatest of these problems is the fluctuation of the symptomatology, which becomes obvious during prolonged observation of reactions to various factors. Voluntary motor activity, emotional stress, pain and acute illnesses frequently augment abnormal motor activity. Whatever increases the intensity of central-nervous-system activity enhances the symptomatology. Consequently, any attempt at measurement must, and does, fall far short of the mark.

Attempts have been made by a number of workers to evaluate alterations in spasticity, rigidity and hyperkinesia by electromyographic tracings.[39-41] Although character of discharge is of pathophysiologic interest, quantitative comparisons between tracings is of questionable value. By assiduous effort the number of variables influencing the size of the potentials may be considerably reduced, but the remaining error is no less than that inherent in careful clinical estimation. Hence simultaneous EEG and EMG recording was used to supplement clinical observation. Results indicated that though the method is better than the isolated EMG tracing, it is still only partially satisfactory.

Oral administration was preferred for the primary study to permit comparison with other oral studies and to obtain more prolonged effect. The use of capsules permitted exact placebo duplication without taste effects. The dose was chosen as a mean between the extremes previously employed by others. The 5 gm. given daily was the maximum dose used successfully by Berger and Schwartz.[41] The hours of administration were arranged to cover both the active period of the day and the hours during which electrical studies were performed. In view of the limited quantity of the drug available at the time, it was deemed advisable to treat a smaller group over a longer period (five weeks) in order to observe any development of tolerance.

In this series Mephenesin had some effect in some cases both orally and intravenously. However, the nature of the effect differed from case to case. When the drug was effective, the change was apparent within forty-eight hours of initiation of oral therapy. The effect was greater, though transient, when the intravenous route was employed. The nature of response remained constant regardless of the mode of administration. It appears from our data that a fairly accurate index of oral effectiveness can be obtained through a preliminary three-day trial consisting of 5 to 6 gm. per day by mouth in tablet or capsule form at intervals of three or

four hours during waking hours. Larger doses are generally ineffective and may cause leukopenia. Intravenous injection of Mephenesin, although apparently safe in the concentrations we used, is of little practical importance.

The period of treatment proved too short for the development of tolerance to be estimated.

In the evaluation of curare in oil cited above,[2] the extreme suggestibility of the paraplegic patients under observation was emphasized. In this study, therefore, all possible precautions were taken to minimize this effect. That it remained is indicated by the "toxic symptoms" in the control group receiving placebos. The symptoms noted were similar to those reported by earlier observers.

All blood and urinary studies were negative. The absence of venous thrombosis, hemolysis and hemoglobinuria[47] may be attributed to the lower concentration of the drug (2 per cent), innocuous solvent (physiologic saline solution) and slow administration.

The estimates of the observers about whether the patients received Mephenesin or placebo were correct in 18 cases and incorrect in 12. In the 15 patients receiving Mephenesin 7 errors were made. Six of these errors were based on the absence of any objective or subjective changes, and though the seventh patient complained of nausea and vomiting, there was no other change in his status. In the 15 patients receiving placebos, 5 errors were made; all were due to the observers' being misled by "toxic symptoms" to conclude that the patients were receiving Mephenesin. The score of correct estimates may be entirely fortuitous; the poor score may be referable in part to the errors inherent in the methods used but far more to the variability of response to the drug and to suggestibility of the patients.

The site of action of Mephenesin in man is as yet incompletely studied. The clinical findings in the literature and in this study yield only inferential information. We agree that effective concentration of the drug may abolish some forms of hyperkinesia and rigidity without narcosis or loss of motor power. The lack of effect on spasticity noted in our series is in conflict with other reports, but this may be due in part to difference in terminology.

Summary and Conclusions

Thirty hospitalized patients with chronic neurologic disorders were selected from a large service for evaluation of oral administration of Mephenesin (Myanesin). The average age for the series was forty and seven-tenths years; the average duration of illness was thirteen and four-tenths years. Fifteen patients received 1 gm. of Mephenesin powder in capsules five times daily for five weeks; the other 15 served as controls. All possible precautions were taken to obtain an objective estimate of clinical response. Laboratory studies included complete blood counts, urinalyses, blood urinary nitrogen and fasting blood sugar determinations before, during and after treatment. Electrical studies consisted of a series of combined electroencephalographic and electromyographic tracings, which were continued in most cases until sleep records were obtained. After oral administration, 7 patients were given a 2 per cent solution of Mephenesin in physiologic saline solution in doses up to 67 mg. per kilogram of body weight. Blood and urinary studies were performed for hemoglobinuria and hematuria, and electroencephalographic and electromyographic tracings taken throughout the infusions.

There was subjective and objective improvement in 6 patients in the series receiving the drug by mouth, 5 in the treated group and 1 in the control group. One patient was made worse. Ten had one or more "toxic symptoms"; 6 of these were in the control group. The symptoms included flushing of the face, nausea, dizziness, vomiting, urinary urgency, weakness, generalized pruritus, anorexia, tinnitus and weight loss, and were similar in control and treated groups. Five patients who received Mephenesin intravenously were improved, and 2 were made worse. Clinical usefulness of this mode of administration was limited by the short duration of effect. Toxicity was evidenced by flushing, scleral injection, horizontal and vertical nystagmus, itching, drowsiness and dizziness. Blood and urinary studies were negative throughout. Results of the electrical studies generally paralleled the clinical findings and indicated that improvement associated with Mephenesin is concurrent with physiologic relaxation or sleep.

Improvement was seen in varying degree in some cases of myoclonus epilepsy, Huntington's chorea, decorticate rigidity, rigidity of multiple sclerosis *and* post-traumatic transverse myelitis and syringomyelia. No improvement was seen in dystonia musculorum deformans, Parkinsonism, double athetosis or Wilson's disease. Response was unpredictable and appeared to depend in part on individual susceptibility. A three-day therapeutic trial of 1 gm. of Mephenesin by mouth five times a day provided an accurate index of effectiveness in spasticity, rigidity and hyperkinesia in this series. No conclusions can be drawn from this study on the development of tolerance to the drug.

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MEDICAL PROGRESS

SEASON, NUTRITION AND PELLAGRA (Concluded)*

FREDERICK SARGENT, II, M.D.,† AND VIRGINIA W. SARGENT, M.S.

CHICAGO, ILLINOIS

Other reports from Southern nutritional research groups independently confirm these trends in intakes of components of the vitamin B complex and suggest that the population receives the best nourishment just before clinical symptoms of malnutrition appear. Darby et al.,[27] working in the same Tennessee community as Steinkamp and her associates,[17] found that the urinary excretion of thiamine by pregnant women on the average was higher in the late winter and early spring (the seasons here have the usual designation) months, corresponding to the season of high pork and dried legume intake.‡ Although these two studies reveal that in the late winter and early spring the sample Tennessee groups were consuming relatively large amounts of nutritious food, sharply contrasting clinical observations were made at the Hillman Clinic in nearby Birmingham, Alabama,[29] where February, March and April were the months in which symptoms of nutritive failure most frequently began. Clinical admissions were maximal in June. Since nutritive failure is principally due to a deficiency of components of the vitamin B complex, the problem posed by analysis of Goldberger's data is once more encountered.

To explain these seemingly paradoxical observations, we offer the hypotheses that the nutritive requirements of the tissues are conditioned by the seasonally changing metabolic status of the human being and that the response of the bodily organs to ingested food changes from season to season.

A Theory of Seasonal Variation

Both these hypotheses are embodied in the theory of Edmund Hughes,[30] a practicing English physician. Although the theory was published almost twenty years ago, few workers seem to be familiar with it. The theory, it should be understood, was developed independently of an extensive familiarity with the

*The opinions expressed in this paper are those of the authors and do not necessarily represent the official views of any governmental agency.

†Clinical instructor in medicine University of Illinois College of Medicine; medical officer (internal medicine), Medical Nutrition Laboratory, Chicago, Illinois, an installation under the jurisdiction of The Surgeon General, Department of the Army.

‡Hou[28] has reported that 20 normal Chinese likewise excreted more thiamine in the winter than in the summer.

literature, and its predictions have never to our knowledge been examined in the light of accumulated nutritional knowledge. This theory states "That human physiology, in common probably with that of all other mammals, was built upon the expectation of annual inactive periods, that is on the expectation of seasonal sleep, together with what this involves; and that, in a heat-stable mammal, such as man, traces of the chemico-physiological rhythm implied by this may still be present under appropriate physical and other conditions."[30] It was on the basis of deductions from this theory that Hughes predicted the seasonal variation in the incidence of diseases due to "deficiency of unreserved substances" in general and in pellagra in particular. The novel implication of this theory is that there exists in human physiology a vestigial functional process (a chemistry or mechanism of season), which is pictured as "a coordinate physiological trend in the sense of readjustment and difference of degree among processes proper to the organism at all times."[30] For such a function to have survived, its fundamental character must not have become harmful to its possessor, the structures originally concerned with this character must have survived to a sufficient degree without important changes in their chemistry or uses in the organism, and the external stimuli and their sequences, which were required to activate the original function, must continue. This functional character will have almost but not entirely lost its original value, tend to be more energetic in infants than in adults, differ in degree of manifestation among persons and tend to declare its presence by morbid signs and symptoms if the patient deviates persistently or markedly from the "natural" mode of life — that is, from that imposed by natural circumstances on uncivilized man.

Such a vestigial functional cycle, therefore, will proceed normally if its requirements are met over the year, will proceed abnormally if there is a noncompliance in part or whole of its course, and will cease functioning only if and where its causes cease to act.

Essentially, this seasonal cycle is a nutritional cycle, for the expectation of seasonal inactivity in the primitive mammal implies expectation of an annual period of food deprivation and tissue rest. Thus, by analogy to hibernation, the year may be divided into two phases: the anaphase* extending from April through September and the cataphase* extending from October through March. The anaphase corresponds to the original period of "activity and physiological preparation for complete deprivation of food accompanied by the degree of functional rest attained in deep sleep."[30] The cataphase corresponds vestigially to "the realization of the state prepared for, and, toward its end, a physiological preparation (by maturation of gonads, etc.) for reproductive and general activity."[30] Since it is a nutritional cycle, abnormalities will develop if its nutritional demands are not met. Consequently, granting the existence of the cycle, human food requirements will be influenced by these demands. Furthermore, the expectation of complete food deprivation (an expectation on which the vestigial cycle is founded) will alter the response of organs to ingested food, especially the gastrointestinal tract. Nutritive substances may be classified according to their *relative* tendency to be stored in the organism. Reserved substances, including fat and fat-soluble vitamins, will tend to be handled as a group; and unreserved substances, including protein and the water-soluble vitamins, will tend to be handled as another group.

One other important point in Hughes's theory concerns the external stimulus: the ultraviolet portion of the solar spectrum. Seasonal exposure of men to the influence of solar radiation of sufficient intensity will produce physiologic changes, which will be partly adjustive and partly preparative for seasonal inactivity (these latter changes will be vestigial in degree). The complete cycle may be expected to occur only in regions where physical conditions appropriate to both its phases will be alternately imposed year after year — for example, the northern and southern temperate regions.

On the basis of his theory Hughes made a number of predictions concerning the metabolism of reserved and unreserved substances. Predictions pertinent to the present discussion are outlined in Table 3. The tabulation has been divided into three parts: food in general, reserved substances and unreserved substances.

The theory demands greater food intake during the anaphase than during the cataphase and foretells, during the latter, somewhat reduced digestive capacity to all foods. Except for fat intake, the mill operatives of the village studied by Goldberger consumed more calories, carbohydrate and protein during the cataphase than during the anaphase. This behavior may have been brought about by and increased appetite for readily oxidizable food — carbohydrate — induced by the calorigenic demands of winter.[31] The secondary increase in fat consumption during the winter might be similarly explained. Such an environmental influence on man is perhaps seen in the finding of some investigators that the basal metabolic rate is increased during the winter months.[32]

During the anaphase Hughes's theory states that reserves will be acquired to be stored against the anticipated period of food shortage. An expression of this phenomenon might be the increased consumption of fat in the summer. Another expression would be an increase in body weight during the anaphase. Although there are no data available on the body weights of the population of the village

*Hughes refers to the anaphase as Phase A and the cataphase as Phase B.

studied by Goldberger, an annual anaphasic gain in weight is an established fact for the population in general.[2] Whether or not the anaphasic increase in body weight is due to storage of fat has not been established for human beings, but Hughes[30] remarks that it has been "the experience of meat-dealers that the fattest carcasses are met with in October-November, the leanest in April-May." During the cataphase the organism will tend to maintain cell nutrition slightly more on reserved than on unreserved substances. This tendency will cause consumption of stores of reserved substances, and either body weight will decrease or the rate of gain will diminish. Such a phenomenon actually occurs in the population in general.[2]

TABLE 3. *Hughes's Predictions on Metabolism of Reserved and Unreserved Substances.*

ANAPHASE	CATAPHASE
FOOD IN GENERAL	
1. Health is served by relative abundance of food.	1. Health is served by a relative shortage of food. 2. Digestive capacity will be lowered to all classes of foodstuffs.
RESERVED SUBSTANCES	
1. Reserves acquired will be substances (fat and associated substances) capable of storage against a period of expected deprivation. 2. Body weight will increase. 3. Requirement for fat-soluble vitamins will decrease.	1. Organism will maintain cell nutrition slightly more on reserved substances than on unreserved substances. 2. Body weight will decrease. 3. Requirement for fat-soluble vitamins will increase, especially with continued activity.
UNRESERVED SUBSTANCES	
1. Organism will maintain cell nutrition slightly more on unreserved substances, which are chiefly burnt during activity. 2. Requirement for water-soluble vitamins will increase. 3. Consequences of a deficiency of unreserved substance will occur chiefly in anaphase. 4. A defect physiologic for cataphase may be pathologic for anaphase. a. Mild defect in anaphase might undergo remission in in cataphase and relapse in succeeding anaphase. b. Severe defect on both phases may be accentuated or become acutely manifest in anaphase. There will be no recovery in cataphase.	1. Unreserved substances acquired during anaphase are spared to the utmost because of decreased tissue requirement and decreased tissue demand.

The metabolic demands for reserved substances will be diminished in the anaphase and increased in the cataphase. Accordingly, the requirement for vitamin A should be slightly reduced in the summer. In growing calves, it has been shown that the vitamin A requirement is greater in the winter than in the summer.[33] Evidence for a similar seasonal variation in the requirement for vitamin A by man has been presented by Rapaport, Herman and Lehman[34] in a study of 6 cases of ichthyosis. This phenomenon, therefore, suggests that there should be a seasonal variation in diseases attributable to vitamin A deficiency. The facts support this suggestion, for the maximum incidence of vitamin A deficiency occurs between January and May (Table 4). The theory, furthermore, demands that reserved substances will be handled metabolically as a group. Thus, the incidence of other diseases due to deficiency of reserved substances should be maximal in the cataphase. Accordingly, the incidence of vitamin K deficiency, rickets, tetany, osteomalacia and dental caries is maximal during the cataphase (Table 4).

The anaphase, according to theory, is a phase of expected activity. During this period, tissue demands for unreserved substances are increased because the organism will maintain cell nutrition slightly more on unreserved substances, which are chiefly required during activity. Consequently, the effects of a deficiency of unreserved substance will occur chiefly in the anaphase. Whereas a defect might be physiologic for the cataphase, it will be pathologic for the anaphase. Mild anaphasic deficiencies may clear up in the cataphase only to recur in the next anaphase. On the other hand, when the deficiency of unreserved substance prevails throughout the year, the clinical symptoms are accentuated or acutely manifest in the anaphase and ameliorated in the cataphase. The implications of these propositions is that tissue re-

TABLE 4. *Season and Incidence of Diseases of Nutritional Deficiency.*

DISEASE	AUTHOR	MAXIMUM INCIDENCE
Anaphase (April–September):		
Pellagra	Grimm[35]	May–June
	Jobling and Petersen[36]	June–July
	Siler and Garrison[37]	July
	Spies et al.[38]	June
	Harris and Harris[39]	May–June
Scurvy	Park et al.[40]	September–October
	Wimberger[41]	May–August
	Dogramaci[42]	June–August
	League of Nations[43]	June
	McMillan and Inglis[44]	June
	Vilter et al.[45]	May
Beriberi	Aykroyd[46]	May
	Stepp and György[47]	July–September
	Albert[48]	December
	Hou[28]	July–October
Ariboflavinosis	Spies[49]	June
Nutritive failure	Spies[29]	June
Cataphase (October–March):		
Vitamin A deficiency	Blegvad[50]	March–April
	Sweet and K'ang[51]	January–March
	Widmark[52]	January–May
Vitamin K deficiency	Kerpel-Fronivs et al.[53]	Winter
Rickets	Ferguson[54]	December–April
	Follis et al.[55]	Winter
	Hortsmann and Petersen[56]	March–April
	Hess[57]	Winter
	Schmorl[58]	Winter
Tetany	Chu and Sung[59]	March–April
	Guild[60]	March
	Horstmann and Petersen[56]	March
	Japha[61]	Spring
	Moro[62]	Winter
	Shelling[63]	Winter
	von Frankl-Hochwart[64]	March–April
	Hess[57]	Spring
Osteomalacia	Hess[57]	Winter
	Hume and Nirenstein[65]	January–April
	Miles and Feng[66]	Winter
Dental caries	Erpf[67]	January
	Lathrop[68]	January
	McBeath[69]	Winter–spring
	McBeath and Zucker[70]	Winter–spring
	American Dental Association[71]	Winter

quirements for unreserved substances will be greater in the anaphase than in the cataphase. There is little experimental evidence concerning seasonal changes in the requirements for the B vitamins. One investigator,[72] in a poorly controlled and inadequately documented study, reported that pigeons on a beriberi-producing diet developed mild symptoms more rapidly (seventeen to twenty days) when fed this diet between October and February than when fed the same diet in the summer (fifty-seven days). In contrast, there is abundant evidence that nutritional diseases due to lack of unreserved substances — pellagra, scurvy, beriberi, ariboflavinosis and nutritive failure — reach a maximum incidence in the anaphase (Table 4).

Nutrient Requirements and Interrelations

Goldberger's data on food used and the incidence of pellagra permit an examination for evidence of seasonal changes in requirements for pellagra-preventive factors. To make such an examination limits must be established for the requirements for unreserved substances concerned in the etiology of pellagra. A deficiency or imbalance of the following factors is basic in the development of pellagra in men subsisting on a diet containing corn: animal protein of good quality, niacin, interrelations of the vitamin B complex and the composition of the diet.[5] The population of the village studied by Goldberger consumed a corn diet (about 15 per cent of the total daily calories were derived from corn meal). The consumption of animal protein of good quality should exceed 30 gm. per day "to prevent pellagra on a corn diet containing no green vegetables, adequate amounts of riboflavin and minimum of 4 mgs. of nicotinic acid."[5] The intake of animal protein by the mill operatives ranged from 7.8 to 11.6 gm. per day — a definitely low range. The consumption of green vegetables was seasonal, ranging from 1.0 to 4.6 gm. per day in the period December to April to 10.4 to 52.7 gm. per day during the remainder of the year. The maximum (52.7 gm. per day) occurred in August. Even an intake of 2 oz. of green vegetables a day is small indeed and does not contribute much to the nutrition of the subject. As shown above, the intake of riboflavin was low throughout the year.

Thus far the evidence points to a submarginal intake of pellagra-preventive nutrients. The calculated intake of niacin, on the other hand, seemed better. Frazier and Friedemann[5] conclude from their study of pellagra that the requirement for this nutrient by persons on marginal diets containing corn products is probably about 7.5 mg. per day. In the village studied by Goldberger this minimum level was exceeded in only four months — December, January, February and March — ranging during this interval from 8.0 to 8.3 mg. per day. During the remainder of the year, the intake was below 7.5 mg. per day, varying between 6.0 and 7.3 mg. Since the diet of the population was submarginal from the point of view of the intake of other nutrients, as mentioned above, it seems likely, in spite of the fact that the calculated intakes of niacin did not deviate widely from the 7.5-mg. level, that the niacin intake was deficient. The thiamine intake by the population of the village was adequate throughout the year. These considerations suggest that the mill-village population probably consumed no better than marginal diets throughout the year.

A consideration of the interactions of animal protein of good quality (tryptophane), riboflavin and corn meal (pellagragenic factors) on niacin requirements suggests that the mill-village households consumed marginal diets. Additional interactions of nutrients are known that might bear on this problem. Although many of the data available[73] are based on animal experimentation and are not directly applicable, one commonly held belief deserves review: that the requirement for a component of the vitamin B complex, especially thiamine, varies with the caloric intake. A variety of formulas have been developed for describing this relation. Whether such a relation actually exists for human beings has never been demonstrated. Writing on this problem, Keyes et al.[74] state:

> We question whether the thiamine requirement is actually strictly and linearly proportional to the calories or even to the non-fat calories. The evidence for this common assumption is not very satisfactory even in animal experiments and there is extremely little basis for presuming such an exact relation in man. If we merely examine all the available evidence without prejudice then we should probably conclude that signs of thiamine deficiency are apt to appear within some months when the thiamine intake is less than 0.61 mgm. per day, regardless of calories. It is possible that the actual thiamine requirement may be a constant plus an amount proportional to the total or non-fat calories. . . .

Now, if the human requirement for components of the vitamin B complex should vary with caloric intake (total calories or nonfat calories), such a phenomenon might help to explain the somewhat paradoxical relation found between food intake and pellagra. During the prepellagra season one would expect an imbalance in the ration of niacin or thiamine to caloric intake: fewer milligrams per 1000 calories should be consumed than during the period prior to the beginning of the epidemic wave of pellagra. Such an imbalance would constitute a deficiency. What are the facts? The facts are given in Figure 4, showing, as scatter grams, the relation between calculated caloric intake and calculated intake of niacin and thiamine. The ordinate shows the monthly caloric intake as calories per day per adult male unit and the abscissa, the niacin and thiamine intake as milligrams per day per adult male unit by the mill operatives of the village investigated by Goldberger. The calculated vitamin intake has been related to the calculated intake of total calories and nonfat calories. The open circles represent the months (November,

December, January and February) when no pellagra was found. The closed circles represent the months when cases of epidemic pellagra were present. In every case the vitamin intake increased with increasing caloric intake. This relation, which is especially noteworthy in the lower scatter grams relating vitamin intake to nonfat calories, demonstrates that no vitamin-calorie imbalance occurred. Interesting is the fact that the ratio of niacin to calories actually increased in November and December — the two points deviating most widely in the upper and lower left-hand scatter grams. The conclusion, then, must be that, so far as interpretation of Goldberger's data is concerned, a vitamin-calorie interrelation is not involved.

These facts establish that the mill operatives tended to consume a pellagra-producing diet the year around. Although, according to the calculations, the population was consuming *relatively* the best diet when pellagra began and *relatively* the worst diet when pellagra disappeared, at no time did changes in the intake of nutrients occur — even such changes as would have been expected if dietary deficiencies alone were causing the seasonal wave of pellagra. Evidently, then, some factor or factors must have been conditioning the tissue requirements for the pellagra-preventive factors. The facts of our analysis suggest that the requirements for pellagra-preventive factors are greater in the spring and summer than in the autumn and winter — that is, greater in the anaphase than in the cataphase. Just such a relation between season and requirements for unreserved nutrients has been predicted by Hughes (Table 3). In the cataphase the requirements for unreserved substances are reduced because the tissues expect rest; in the anaphase tissue demands for these substances are increased because activity is expected. Consequently, as indicated above, when the deficiency of unreserved substances prevails throughout the year, the clinical symptoms are accentuated or acutely manifest in the anaphase and ameliorated in the cataphase. The rapid rise and fall of the incidence of pellagra is just such an acute manifestation. Since Goldberger's data concerned only new cases, the rapid subsidence of the seasonal wave of pellagra after June probably meant that the majority of the pellagra-susceptible persons in the mill-village population were sufficiently deficient in unreserved substances to develop pellagra early in the anaphase. The others, in whom the deficiency was not so great, were those whose nutrition was better. Consequently, pellagra developed more slowly. These cases appeared in the late summer and early fall. Their presence was indicated by the break in rapid decline of the pellagra wave that took place in August and September.

Factors other than Hughes's vestigial mechanism may have played a part in the seasonal wave of pellagra in the village in Goldberger's study. Tissue demands for nutrients are increased by various "conditioning factors," two of which may have been operative in the mill-village population — growth and pregnancy. Over 90 per cent of the cases of pellagra in the village occurred in children aged two to fourteen years (67 per cent) and women in the child-bearing age (24 per cent). So far as growth is concerned, the spring accentuation that occurs in normal children[2] fails to occur in malnourished children. Dreizen, Mann and Spies[75] have reported that among children in nutritive failure retarded growth is most frequent in June, July and August. Thus, as would be expected, retarded growth, like pellagra, can be correlated with the anaphasic increase in tissue requirements for nutrients. Regarding pregnancy, we can only speculate, for no data are available on the number of women who were actually pregnant in the village. According to Huntington[76] the birth rate in South Carolina varies seasonally and has a summer maximum.

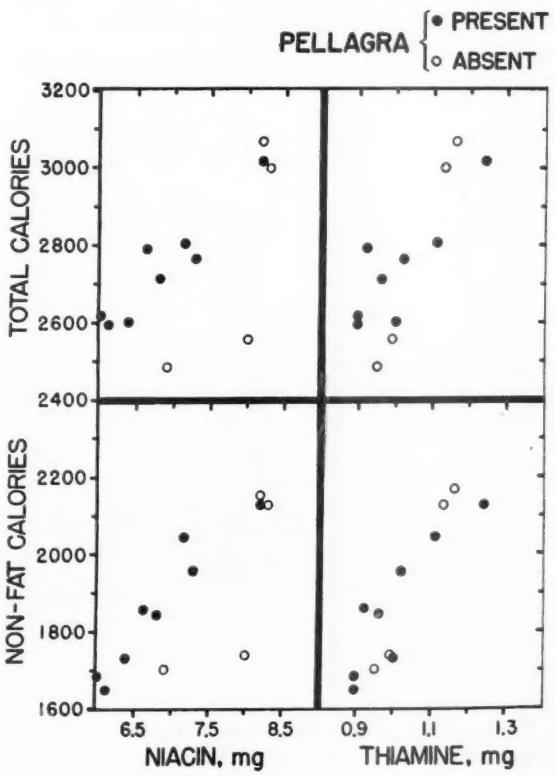

FIGURE 4. *Calculated Monthly Intake of Niacin and Thiamine in Relation to Calculated Monthly Caloric Intake: Total Caloric and Nonfat Caloric Intake.*

In each case the units are expressed as quantity per day per adult male unit. The open circles represent months when pellagra was absent — November through February; the closed circles represent months when pellagra was present — March through October. (Data calculated from dietaries of Goldberger et al.[4])

Since it is known[13] that pregnancy increases the need for all nutrients and since that demand is greatest in the third trimester, it follows that pregnancy may have been a contributing factor in the acute outbreak of pellagra in the mill village. Since most of the cases of pellagra occurred in persons who were not workers, it is difficult to conceive how seasonal changes in physical exertion may have contributed significantly to the spring

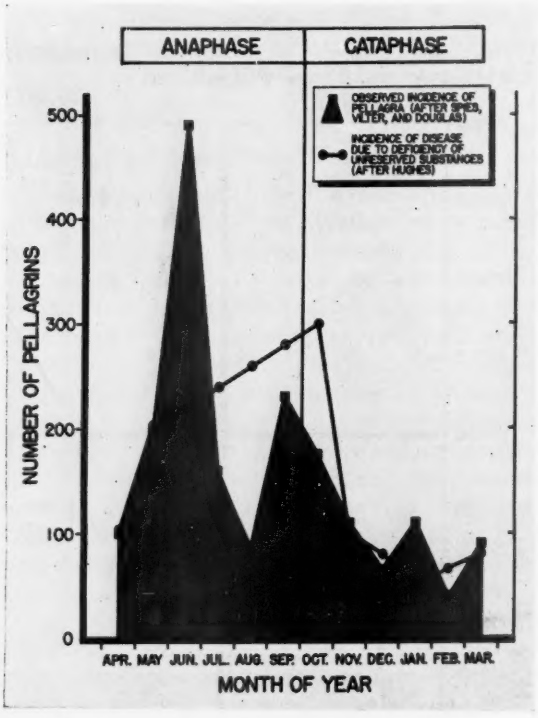

FIGURE 5. *Comparison between Observed Seasonal Incidence of Pellagra (Spies, Vilter and Douglas[38]) and Predicted Incidence of Diseases Due to Deficiency of Unreserved Substances (Hughes[30]).*

outbreak. The factor of sunlight is considered below.

Examination of the curves representing the seasonal incidence of pellagra reveals two fundamental characteristics: a steep and continuous climb from onset to peak and a biphasic decline — a rapid decline for one or two months followed by a slower decline for another month or two (Fig. 3). This break in the incidence curve usually occurs in September. The significance of the break is brought out by the fact that, in some populations, the break has actually developed into a definite secondary maximum in September-October.[36, 38, 39, 77] Although such a secondary maximum did not appear in the mill village under discussion, one did develop in several of the other 24 mill villages studied by Goldberger[4] in 1917. Figure 5 illustrates a seasonal variation in pellagra, showing both the primary and secondary maximum levels. The shaded area represents the incidence of pellagra as reported by Spies, Vilter and Douglas.[38] The line indicating incidence predicted from theory has been taken from Hughes.[30] This curve represents, according to Hughes, the expected seasonal variation of diseases due to a deficiency of unreserved substances when that deficiency occurs in both phases. The units are arbitrary. According to the theoretical curve, the deficiency is seen as becoming more and more severe up to the end of the anaphase. In the unmanaged case such a situation might actually develop. In a population under medical care, the waves shown in the shaded area might be expected. In the majority of the pellagra-susceptible population, the disease would develop early in the anaphase coincident with the first stresses of increased tissue demands. During the remainder of the anaphase persons whose nutrition was sufficient to buffer the demands of the increased requirements for a while, but was not sufficient to meet sustained demands, would gradually succumb to the disease. Depending on the size of this latter group, there might be expected to occur, in September-October, either a break in the rate of disappearance of pellagra from the population or a definite secondary maximum.

The operation of the vestigial functional cycle might be a factor in the seasonal behavior of the Yugoslavian population observed by McDougall.[78] This investigator reports that village dietaries, consisting mostly of vegetable foods, show a considerable seasonal variation. The winter diet is monotonous and inadequate. In all seasons the basic ingredient is bread, and in winter little besides bread and dried beans is eaten. Some meat may be eaten on feast days and on Sundays, depending upon the economic status of the different families. After the Christmas season there is often a shortage of wheat for bread. The diet at this time consists of small amounts of pig flesh and bread. Vegetables, fruits, milk and eggs are scarce or unobtainable. "The food is cut down to two restricted meals a day, or even in the case of the poorest peasants to one meal a day; and *the peasant family sleeps much of the time* [italics ours]."[78] In the spring the diet is even poorer with the exhaustion of the supply of pig meat. At this time the diet consists of little more than bread and dried beans. Outbreaks of symptoms of deficiency disease are most commonly seen in the spring.

"From all parts of Yugoslavia cases of rickets, night-blindness, scurvy, pellagra and anemia have been reported. . . ."[78] In the summer, supplies of fruits and vegetables are available, but a shortage of animal protein and fats continues. With autumn the dietary becomes adequate in all respects. This is the period of hardest physical work for the peasants, so that the energy value of the diet is also at its highest level in the summer and autumn.

Here is a population group that exhibits an annual period of relative seasonal inactivity — the winter "sleep." In the spring, food supply does not parallel tissue demands: the supply remains inadequate. Early in the anaphase malnutrition breaks out. As the food supply inproves, the defect is balanced and malnutrition disappears.

Environmental Stimulus

The existence of the mechanism of season depends, among other things, upon the operation of an environmental stimulus. Hughes[30] has suggested that the seasonal variation of ultraviolet radiation is the necessary stimulus. The stimulation may be a direct action on the organism or an indirect action via the food eaten. What is the role of sunlight in pellagra? The spring outbreak of pellagra has been attributed to the action of ultraviolet light on the person deficient in pellagra-preventive factors. The description given by Smith and Ruffin[79] is representative:

> The reactions which occur after a patient in the deficient state becomes exposed to the sun are dramatic in onset, alarming in severity and not infrequently fatal. The usual story is that a subject who is subsisting on a deficient diet, with many of the vague symptoms . . ., though still able to work, exposes himself to the direct rays of the sun early in the spring or summer. Within a few hours a burning and itching sensation is noted over the exposed areas. This is followed in from twenty-four to thirty-six hours by a fiery red erythematous rash. Vesiculation appears accompanied with induration, dry crusts or secondary infection. The bright red erythema changes to a dull bronze and finally to a deep brown. After the initial erythema the mouth and tongue become red and sore and diarrhea appears. Dementia may develop without warning and is an ominous sign.

These investigators depict the situation as follows: during the winter a deficiency of pellagra-preventive factors gradually develops, exposure to sunlight precipitates acute symptoms and then, with dietary improvement in the summer, the deficiencies are corrected and the incidence of pellagra rapidly declines. This explanation is untenable for the following reasons (at least so far as one can judge from Goldberger's data): the individual intake of animal protein and niacin — especially by pellagrins — is low throughout the year; the intake of these nutrients is *relatively* the highest in by prepellagra season and *relatively* the lowest when the incidence of pellagra begins to decline; and exposure to sunlight is not a necessary event for the precipitation of an acute attack.[39] Some investigators[80] suggest that solar sensitization is a manifestation of a nonspecific reaction to an irritant. We believe that the correlation between sunlight and the incidence of pellagra is a manifestation of the vestigial cycle of Hughes.

In addition to sunlight, temperature is a meteorologic element that varies seasonally. Heat and cold have been shown to influence the need for certain components of the vitamin B complex, but whether cold or heat increases or decreases these requirements has not been settled.[13, 81, 82] In the chick, environmental temperature apparently has no influence on the requirement for niacin.[83] An influence of environmental temperature on human vitamin requirements has not been demonstrated, and, to our knowledge, temperature changes have not been suggested as an explanation for the seasonal occurrence of pellagra. Only experimental study would settle whether sunlight or temperature is the environmental stimulus for the mechanism of season.

Adaptation to undernutrition has been proposed by Mitchell[84] as a physiologic attribute conditioning requirements for nutrients. There is little evidence that such a phenomenon can explain our findings. The fact that pellagra occurred indicates that, on the whole, adaptation was not achieved.

To recapitulate, we have shown that Hughes's theory of season accounts remarkably well for certain aspects of the seasonal variation in food intake, the seasonal incidence of pellagra, the seasonal distribution of diseases due to deficiencies of reserved and unreserved substances, and the reported seasonal variation in requirements for vitamins. This theory raises many new questions, but it also illuminates much of the confusion regarding the significance of seasonal variation in man.

Summary

In this investigation the relation between the calculated monthly intake of pellagra-preventive factors (animal protein, niacin, thiamine and riboflavin) and the monthly incidence of pellagra was examined. The data used in this study were figures for monthly food intake and monthly incidence of pellagra collected by Goldberger and his associates in 1917 in a nutritional survey of the households of a Southern textile-mill community. The analytical data of Frazier and Friedemann served as the basis for calculation of the nutritive value of food consumed by the population studied by Goldberger.

Analysis of the material revealed that the calculated intakes of animal protein, riboflavin and niacin by the mill-village households were low throughout the year, the calculated intake of thiamine was adequate throughout the year, the calculated intakes of animal protein, thiamine and niacin were *relatively* highest when the seasonal wave of pellagra began, and the calculated intakes of animal protein, thiamine and niacin were *relatively* lowest when the incidence of pellagra was declining. The seasonal wave of pellagra, therefore, could not be explained solely in terms of dietary deficiencies.

The conclusion reached is that these facts may be explained by a theory first stated by Edmund Hughes, which postulates that seasonal variation in the metabolism of man is a significant factor in the assessment of nutrition. Because Hughes's

postulated metabolic cycle involves changes in tissue needs for nutrients, experiments on human requirements for such nutrients should extend for at least twelve months.

We are indebted to Dr. Edmund Hughes for reading the manuscript and offering suggestions toward better describing his theory, and to Drs. Robert E. Johnson and Robert M. Kark for their encouragement and helpful criticism during the preparation of this paper.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 36131

PRESENTATION OF CASE

First admission. A seventy-six-year-old man entered the hospital complaining of weakness and abdominal enlargement.

The patient had been in excellent health until four months prior to admission, when he began to have some slowing of the urinary stream and occasional nocturia. Six weeks before admission he noted persistent bloating of the stomach and generalized weakness. His physician found an enlarged prostate, with a urinary residuum of several ounces, and demonstrated bladder diverticula by cystogram. A left hydrocele had been tapped and injected five years previously. The patient had mild exertional dyspnea and orthopnea. There had been a recent voluntary 25-pound weight loss on a reducing diet.

Physical examination showed a well nourished, well developed man. The heart was not enlarged. A loud pleuritic friction rub was heard in the left auscultatory triangle and musical wheezes at the right-lung base. A large irregular abdominal mass, which had the consistence of coiled ropes, was felt in both lower quadrants and extended to the level of the lower ribs on the left side. This mass was not fixed to the skin and was slightly movable, nontender and nonpulsatile. Bilateral inguinal hernias and a left scrotal tumor, which did not transilluminate, were also demonstrated. The prostate was firm and three times the normal size. There was no lymphadenopathy.

The temperature, pulse and respirations were normal. The blood pressure was 140 systolic, 75 diastolic.

Examination of the blood disclosed a hemoglobin of 14.6 gm. per 100 cc. and a white-cell count of 9600, with 65 per cent neutrophils, 21 per cent lymphocytes, 11 per cent monocytes, 1 per cent eosinophils and 2 per cent basophils. The urine had a specific gravity of 1.010 and gave a ++ test for albumin, with many red cells in the sediment. The nonprotein nitrogen was 25 mg. and the total protein 5.5 gm. per 100 cc. The prothrombin time was normal. A stool was guaiac negative. A few colonies of *Proteus vulgaris* were obtained on urine culture. Roentgenographic examination of the chest showed an increased anteroposterior diameter, limited excursions of the diaphragm, and calcification and tortuosity of the thoracic aorta. Plain films of the abdomen revealed a large, indistinct soft-tissue mass in the left midabdomen. Retrograde pyelography was impossible because of intravesicular protrusion of the prostate, but intravenous pyelograms demonstrated normal form and function of the right kidney and no function on the left. On cystoscopy the bladder mucosa was inflamed and contained diverticula. The bowel filled well after a barium enema, but the sigmoid was displaced to the right by the abdominal mass (Fig. 1). A barium swallow demonstrated a hiatus hernia.

FIGURE 1.

On the seventh hospital day a nodular prostate weighing 28 gm. was removed by the perineal route. It showed benign hypertrophy on pathological examination. On the fourteenth postoperative day a catheter was passed into the left kidney pelvis after some ureteral obstruction had been encountered

at 13 cm. The urine aspirated was clear and sterile on culture. Dye injection demonstrated a rotated, hydronephrotic kidney, with marked lateral displacement of the ureter. Indigo carmine was excreted promptly on the right and not at all on the left. The patient was discharged on the fifteenth postoperative day.

Second admission (three weeks later). During this period the patient was active, felt well and gained 5 pounds. He believed there had been a marked increase in the size of his abdomen.

Physical examination revealed no new findings. The abdominal mass appeared to be somewhat larger.

Examination of the blood showed 13.4 gm. per 100 cc. of hemoglobin and a white-cell count of 6500, with a normal differential. The urine had a specific gravity of 1.020 and gave a ++ test for albumin. The sediment contained a few red cells. The nonprotein nitrogen was 28 mg., the total protein 6.2 gm., and the fasting blood sugar 105 mg. per 100 cc.; the serum amylase was 30 units, and the prothrombin time normal. The serum van den Bergh was 0.4 mg. per 100 cc. direct, 0.6 mg. indirect.

On the third hospital day an operation was performed.

Differential Diagnosis

Dr. Fiorindo A. Simeone*: This case concerns the diagnosis of a large abdominal mass. We might consider first the laboratory findings. The urinalysis showed some cellular abnormalities and was consistent with the urinary findings in a man who had benign prostatic hypertrophy, who had instrumentation and who had a prostatectomy. There is no real evidence of generalized renal disease. The blood studies help us a great deal in that the normal white-cell count and differential give evidence that this mass was probably not an inflammatory one. In addition he had had no febrile episodes. He had first a serum-protein concentration that was a little low, but when repeated in the second admission it was close to normal so that we should not attach too much importance to it.

As far as the general physical examination is concerned, the patient had signs in his chest that were consistent with emphysema on a senile basis. I was a little concerned about the loud friction rub because it might have represented an infarct or possibly an early metastasis from the abdominal mass; but the x-ray examination of his chest showed no abnormality consistent with this suspicion so that I am inclined to disregard the loud friction rub. He did have a hiatus hernia, and one wonders if a hiatus hernia rubbing up and down with respirations might produce a friction rub. I suppose that is possible although I have never heard of it. The inguinal hernias may have been promoted by the benign hypertrophy of the prostate necessitating straining at urination, or they may have been aggravated by the fact that the mass in the abdomen left less room for movable viscera, which might go into a hernial sac more easily. I am inclined to discount the tumor in the left side of the scrotum, since I believe it may well represent organization of a hematoma, which may have resulted when his hydrocele was tapped and injected five years before admission.

We come down to the local examination of the abdominal mass, which is described as having the consistence of a coiled rope — presumably a solid irregular mass in the lower abdomen more on the left side than the right. By x-ray examination this mass showed a clear-cut relation to the sigmoid, to the left kidney and ureter and was apparently fixed dorsally but not ventrally.

I think at this time we might ask Dr. Wyman to show us the x-ray films.

Dr. Stanley M. Wyman: The ill defined soft-tissue density is well seen overlying the left lower abdomen and displacing loops of bowel away from it. One film from the pyelogram shows the prostatic enlargement and the absence of function of the left kidney. Another film (Fig. 1), taken with slight rotation, shows the sigmoid being displaced very much medially and upward by this large soft-tissue mass. The colon can be seen in this film again displaced anteriorly. A film from the retrograde pyelogram demonstrates the left ureter displaced far laterally beginning at the midsacrum, and it also shows the twisted, rotated, hydronephrotic left kidney. The mass seems to go beyond the midline.

Dr. Simeone: Could you tell us from the appearance of the renal pelvis whether the mass is intrinsic in the kidney or extrinsic?

Dr. Wyman: I believed that it was extrinsic — at any rate, it did not involve the drainage system of the kidney. It might possibly have involved the cortex although I cannot see any evidence of that.

Dr. Simeone: Can you trace the renal outline at all?

Dr. Wyman: No, I cannot.

Dr. Simeone: Would you be willing, on the appearance of this film, to exclude a primary renal tumor with rapid growth?

Dr. Wyman: I think we could exclude that pretty well although we have all been fooled. I think it is much more likely that the mass rises outside the kidney.

Dr. Simeone: Can you see the spleen in these films?

Dr. Wyman: No, I do not believe I can see the spleen adequately on any film.

Dr. Simeone: Would you be willing to guess whether this is a cystic mass or a solid tumor?

Dr. Wyman: I do not believe one can tell, but I think the mass is retroperitoneal and probably

*Assistant surgeon, Massachusetts General Hospital.

not cystic. I have no good evidence for the latter statement.

DR. SIMEONE: There are the diverticula described on x-ray study, so that this mass is certainly not a large diverticulum of the bladder?

DR. WYMAN: No, that is not a diverticulum.

DR. SIMEONE: From the description of the physical examination of this mass I am willing to guess that it was not a cystic mass but rather a solid tumor not connected with the bladder and probably not an intrinsic part of the left kidney. The mass displaced both the sigmoid and the left ureter, and I think a mass that displaced the ureter to this degree and displaced the sigmoid ventrally was almost certainly a retroperitoneal mass. It probably was largely left sided, not only from the physical examination but also from the fact that the sigmoid was displaced to the right. This mass could not have been an appendiceal abscess, which sometimes starts as an abscess in the right lower quadrant and extends across the brim of the pelvis into the left gutter, because the patient had not shown any signs of inflammation, either from the laboratory studies or from the clinical course. For the same reason I do not believe that this was a large mass associated with diverticulitis of the left colon; in addition, the descending colon was intrinsically normal. I doubt that this was abdominal lymphoma, which I suppose could produce this picture on physical examination, because the patient was not sick enough and showed no blood changes. The spleen was not palpable at any time, and he showed no adenopathy elsewhere. I think that this mass was a tumor of the perinephrium, of the space surrounding the kidney and ureter and extending down to the level of the prostate. The most common of these tumors is a lipoma. I do not know if Dr. Wyman would be willing to say whether this density is consistent with a fibrous tumor such as a fibroma or with a lipoma, which is more radiolucent?

DR. WYMAN: It would be hard to say because we are penetrating such an obese patient, but I would think it is more consistent with a fibrous or muscular density than with fat.

DR. SIMEONE: I understand that the roentgenologist can make the histologic diagnosis of lipoma in certain areas of the body. I suppose in this part of the anatomy he cannot. On the basis of statistics I think this tumor was a lipoma that had involved the entire left perinephrium, had extended up sufficiently to displace the kidney, had distorted the course of the ureter sufficiently to obstruct it at the brim of the pelvis and had extended across into the right lower quadrant. The kidney is surrounded by two fatty envelopes, a perinephric and a paranephric, so that there is abundant chance for a lipoma to develop, and to extend along the perinephriums, which communicate across the brim of the pelvis, below the origin of the inferior mesenteric vessels and between the branches of the abdominal aorta. I think lipoma is what this patient had.

The only question for me to answer now is whether this was a benign lesion or a malignant one. Again on the basis of statistics, it was probably benign because most of the lipomas in this area are benign. I would, however, be a little suspicious that this tumor might have had malignant change, for two reasons: first, the tumor had apparently increased in size rather rapidly even in a three-week period while the patient was at home, and second, it had been capable of obstructing the ureter on the left side, at least partially. From what experience I have had with retroperitoneal lesions of all sorts, it is usually the malignant ones that are capable of obstructing the ureter.

In conclusion, I would say that this patient probably had a perinephric lipoma with extension into the right perinephrium, possibly with malignant change.

DR. TRACY B. MALLORY: Dr. Kerr, I believe you operated upon this man. Would you tell us first what the opinion was preoperatively?

DR. WALTER S. KERR, JR.: The tumor was very large and firm. The surface was somewhat nodular, and for this reason I thought that it probably was a lymphosarcoma. My second diagnosis was a fibrosarcoma.

CLINICAL DIAGNOSIS

Malignant lymphoma.

DR. SIMEONE'S DIAGNOSIS

Retroperitoneal lipoma, ? liposarcoma.

ANATOMICAL DIAGNOSES

Retroperitoneal fibromyxosarcoma, low grade.
Lipomas (two).

PATHOLOGICAL DISCUSSION

DR. KERR: At exploration the tumor was found to fill completely the left side of the abdomen and also to extend across the midline under the right lobe of the liver and to extend close to the cecum in the right lower quadrant. In obtaining a biopsy I went through an "outer" capsule, which was about 1 cm. thick and below which was a thin, glistening, transparent capsule. An attempt was made to dissect outside of the "outer" capsule, which at that time I thought was part of the tumor. The obstruction to the left ureter was due to the involvement of the ureter by this outer capsule. In the process of freeing the ureter I entered the plane between the outer capsule and the translucent capsule and delivered the tumor, which weighed about 3000 gm. The pathology report showed no involvement of this outer capsule. Dr. Simeone was partially correct, for there were also two lipomas the size of oranges lateral to the main mass.

DR. SIMEONE: One on the left and one on the right?

DR. KERR: No, they were both on the right. The base of the tumor extended from below the bifurcation of the aorta to the top of the pancreas.

DR. MALLORY: Because of the presence of the two lipomas, we naturally suspected that the third tumor would be a liposarcoma, but we could find no evidence of this histologically. It appeared to be a fibromyxosarcoma of very low-grade malignancy as far as we could make out, still encapsulated but growing with sufficient rapidity so that one could not call it benign.

DR. KERR: After exposing the tumor and getting around its outer thickened capsule we saw no evidence of nodularity. Indurated fat along the colon was closely attached to the tumor and had caused the apparent nodularity.

DR. EDWARD F. BLAND: What has happened to the patient?

DR. KERR: He went back to work in three weeks.

CASE 36132

PRESENTATION OF CASE

A sixty-seven-year-old woman entered the Massachusetts Eye and Ear Infirmary complaining of pain and swelling over the left eye.

The patient was well until six weeks before entry, when, with no previous history of trauma or upper respiratory infection, she noted a tender swelling over the left eye that gradually progressed to involve the eyelid. For a week before admission she had diplopia with one image higher than the other. She had no severe pain, malaise, dizziness, fainting or nausea. For several days she received penicillin from her physician without effect, and then she was referred to the Massachusetts Eye and Ear Infirmary. Local examination in the Out Patient Department revealed a large, fairly firm, nodular mass in the floor and anterior wall of the left frontal bone, with limitation of upward and outward motion of the left eye. A skull plate showed destruction of the left frontal bone involving the outer wall and the outline of the frontal and upper rim of the orbit. This extended outward and backward. The left frontal sinus was full of pus, and there was a fluid level in the right frontal sinus. The patient was admitted to the hospital with a tentative diagnosis of osteomyelitis of the skull.

Physical examination showed a thin woman in no distress. The left eye globe was lower than the right, with slight proptosis. The left frontal area and eyelid were pink and swollen. A hard mass was palpated in the upper rim of the left orbit, with a tender fluctuant area just above it. Both pupils reacted well to light and accommodation. The anterior cervical lymph nodes were palpable on the right. The trachea was in the midline, and the neck was supple. The nose and throat were clear. The heart was slightly enlarged, with a soft, apical, systolic murmur transmitted to the axilla. Examination of the lungs and abdomen was negative as were ophthalmoscopic and neurologic examinations.

The pulse was 88, and the temperature 101°F. The blood pressure was 142 systolic, 86 diastolic.

Examination of the blood revealed a red-cell count of 3,150,000, with a hemoglobin of 10.5 gm., and a white-cell count of 14,400, with 76 per cent neutrophils. The urine was normal. A spinal tap showed an initial pressure equivalent to 130 mm. of water, with normal dynamics. The cerebrospinal fluid contained 118 milliequiv. per liter of chloride, 26 mg. per 100 cc. of protein and 95 mg. of sugar. There were 29 cells per cubic millimeter, 18 of them neutrophils, and 11 lymphocytes. The gold-sol curve was 0001223221, and the fluid was sterile on culture. Blood culture, however, yielded coagulase-positive hemolytic *Staphylococcus aureus*. A chest plate showed emphysema, fibrosis and an elevated left leaf of the diaphragm, which was ascribed to a dilated colon.

On the second hospital day the osteolytic bone, which extended from the coronal suture to the floor of the frontal sinus, was removed, and the patient placed on sulfadiazine and penicillin. On the second postoperative day a ++ sugar test and a few sulfonamide crystals were noted in the urine. On the following day it gave a +++ sugar reaction, and a ++ albumin reaction, and the sediment was loaded with red cells. The temperature, which had fallen to normal, rose to 101°F. Sulfadiazine was discontinued, with subsequent disappearance of the red cells and albumin. On the fifth postoperative day a clonic convulsion began, which started around the face and neck and soon involved the right arm and leg. The temperature remained elevated, and the patient lapsed from a completely lucid state into somewhat clouded consciousness. Minimal left facial weakness was described, but neurologic and ophthalmologic examinations were otherwise negative. A lumbar tap showed an initial spinal-fluid pressure equivalent to 104 mm. of water and yielded clear sterile fluid, with 11 neutrophils and 12 red cells per cubic millimeter, and a negative Pandy reaction. Intrathecal administration of penicillin and streptomycin was begun. On the eighth postoperative day bilateral occipital burr holes were made through which the brain bulged very slightly. No pus escaped, and subsequently there was only slight improvement. Ventriculograms made on the fifteenth hospital day showed poor filling of the right lateral ventricle. A tentative diagnosis of extending osteomyelitis with subdural empyema was made, but catheter drainage of the subdural space yielded no pus. The patient's condition remained very poor, and repeated lumbar taps showed no significant change. Dullness, decreased breath sounds and sticky rales appeared at the left-lung base, and the temperature rose to 104°F. Roentgenograms taken on the twentieth hospital day showed atelectasis and a questionable pneumonia in the left lung. The nonprotein nitrogen remained within normal limits, but albumin and sugar reappeared in the urine, which also contained many white cells in clumps in the sediment.

The white-cell count rose to 32,000, and on the twenty-ninth hospital day the patient died.

Differential Diagnosis

Dr. William H. Sweet*: "On the eighth postoperative day bilateral occipital burr holes were made through which the brain bulged very slightly." There is no mention of whether or not the patient had an electroencephalogram. I should like to draw attention to the utility of that examination in this sort of problem. I have just talked with Dr. Schwab about this procedure, and he says that the electroencephalogram is abnormal in 90 per cent of patients with brain abscess and that it localizes the abscess in half the cases so that this procedure, which does not put any particular stress on the patient, is a rather handy one to use.

We do not know whether the poor filling of the lateral ventricle in the ventriculogram done on the fifteenth hospital day was due to an inadequate amount of air present at the time the film was taken or whether it was caused by a large defect that represented a lesion.

The principal diagnostic problem confronting the patient's physicians here had to do with the possible presence of intracranial infection, its precise locus and the appropriate treatment in case the diagnosis could be made. Going on the assumption that the patient did have a frontal sinusitis that had spread to the region of the frontal bone and caused the typical swelling about the orbit and that later there was spread of this infection or a consequence of this infection to the intracranial cavity, we have then to determine just what was going on in the intracranial cavity and whether or not it was infection. I think the outstanding publication on the subject of subdural abscess or empyema is one that emanated from here, written by Dr. Kubik and Dr. Adams.[1] This article, which was published back in 1943 in the preantibiotic era described the course of events when the clinical picture was not confused by the partially successful effect of antibiotics. The patient who develops pus in the subdural space inside the dura but not in the subarachnoid space has a course that is in many respects very similar to this. This type of infection is likely to follow a chronic frontal sinusitis. It very often follows only after the sinusitis has spread to the bone and there has been a frontal osteomyelitis. It is typical for these patients to develop some swelling around the orbit. Typically, the central-nervous-system disorder is ushered in with one or more convulsions, and the spinal fluid shows a comparatively low white-cell count. The resemblance between the typical untreated picture of subdural empyema and this particular patient's course stops there I think. In the cases that were seen here, the spinal fluid ran a rather higher white-cell count than this but lower than that in meningitis. The white-cell count in the cerebrospinal fluid ranged from 150 to 500 per cubic millimeter in the 14 cases that were reported by Dr. Kubik and Dr. Adams. Furthermore, the total protein in every one of their cases was elevated. Here it was normal — 26 mg. per 100 cc. The patient with an untreated subdural empyema is also exceedingly ill, and in the days before antibiotic treatment, death in some 12 of 14 cases occurred within two to five days of the onset of evidence of involvement of the central nervous system. Since the advent of antibiotic therapy, this clinical picture has been materially confused by a reduction in the severity of the clinical picture, and we are left with great difficulty in determining whether or not there is any pus in any portion of the subdural space and, if so, in determining just where the pus is.

In the subdural space the pus has a tendency to flow slowly around so that it may appear on the orbital surfaces of the frontal lobe, or along the medial surface of the hemisphere, or it may dissect its way down into the subarachnoid sulci getting out of the subdural space and pocketing in the subarachnoid space. I have been quite disappointed on two occasions to drain a subdural empyema, I thought satisfactorily, with catheters scattered about over the superior lateral surface of the hemispheres, only to have the patient die abruptly after a period of improvement. The post-mortem examination revealed pus on the medial and inferior surfaces of a cerebral hemisphere. I think that in a case of the sort under discussion those handling the patient must have been very much concerned lest such a situation be present. I wonder if Dr. Mallory could find where they did try to drain that subdural space. They may well, of course, have put their catheters in underneath the hemisphere or along its medial surface in an attempt to exclude infection there, and if they did so, I think they did all one can do to exclude this possibility.

The possibility of a brain abscess is, I think, comparatively small here. We know that this lesion was severe enough to cause the patient to be in a state of clouded consciousness and to be very ill, and yet the cerebrospinal-fluid pressure was normal and there were essentially no localizing signs with the exception of the minimal facial weakness and the one seizure that involved the face, the right arm and leg. I should anticipate that, if there were a cerebral abscess in this patient, it would have been large enough to have been apparent on a ventriculogram.

I have already alluded briefly to another type of localization of pus in the intracranial cavity localized in the subarachnoid space, deep in the cerebral sulci. There is a recent article by LeBeau,[2] from la Pitié in Paris; he is the first, I think, to present a whole series of cases in which pus was localized to sulci over a comparatively small area over the hemispheres, presenting an exceedingly difficult diagnostic problem and yet an exceedingly

*Associate visiting neurosurgeon, Massachusetts General Hospital.

important one because if the pus is removed from that region the patient has an excellent opportunity to recover.

There is still another type of disorder that develops when pus invades the frontal bone, and the disorder spreads from there into the intracranial cavity; namely, thrombosis of the cerebral veins or the superior longitudinal sinus. This is often seen in connection with subdural abscess or empyema. The occlusion may not be due to obviously septic emboli, and a number of cases show only blood clot occluding the superior longitudinal sinus in its anterior half along with a number of cerebral veins. These alone may be a cause of death. I think we have to consider that possibility very seriously as accounting for a great deal of this patient's intracranial disorder. Such a diagnosis is in accord with the slight elevation in the white-cell count in the cerebrospinal fluid here, as well as the other cerebrospinal-fluid findings. In particular, the normal cerebrospinal-fluid sugar would be consistent with this diagnosis. As I say, this is a common sequel to an operative infection of the frontal bone. The circulation of the blood between the venous diploe of the cranium and the veins in the cerebral cortex is one with many anastomoses. The venous pressure there is low, and there is an excellent opportunity for the passage of septic emboli to the brain or for venous stasis and thrombosis to develop. Since I must make a guess about the pathologic process in the intracranial cavity, I shall assume that those handling this patient had probably excluded subdural empyema or intracranial abscess to the best of their ability and that the patient's intracranial disorder was on the basis of an extensive thrombosis of cerebral veins and possibly of the superior sagittal sinus.

Terminally, I think it was suggested that she also had pulmonary and genitourinary infection, and from the evidence of the sugar in the urine when the infection got out of hand, I think it is probable that the patient also had a mild diabetes mellitus. I do not think the glycosuria is likely to have been due to direct cerebral involvement. I must say that I find such cases an extreme problem when I am called upon to handle them, and I believe that in a case of this kind, despite the fact that one would have to explore through an infected field where the lesion on the frontal bone had been removed, I believe that one should exclude the possibility of pus over either frontal lobe in the same fashion since the areas are sites of predilection for the spread of pus after infection of the frontal bone or sinus, or both.

Clinical Diagnoses

Osteomyelitis of skull.
Congestive heart failure.

Dr. Sweet's Diagnoses

Thrombosis, extensive, cerebral veins.
?Thrombosis, superior sagittal sinus.
Infection, lungs and genitourinary tract.
Diabetes mellitus.

Anatomical Diagnoses

Renal-cell carcinoma, papillary type, of left kidney, with metastases to skull, meninges, lungs and bronchial, periaortic and perirenal lymph nodes.
Strangulated ileum due to peritoneal adhesions.
Bronchopneumonia, organizing, bilateral.
Cortical adenoma of adrenal gland.
Adenoma of thyroid gland.
Leiomyomata uteri.
Fibroma of ovary.

Pathological Discussion

Dr. Tracy B. Mallory: I think this was an exceptionally blind case. Dr. Sweet's line of reasoning was that of the physician who took care of the patient on the ward, but our findings were entirely different. She had a large tumor of the lower pole of the left kidney, a renal-cell adenocarcinoma, and the area of destruction in the skull was due to metastatic neoplasm. The frontal bone was not submitted to our laboratory for histological examination until after the patient's death. At autopsy it was found that the meninges were diffusely infiltrated with carcinoma, the most marked areas being over the frontal lobes and about the anterior portion of the falx. There also was tumor in the dura of the middle fossa. The superior longitudinal sinus was clear, and no tumor foci were found within the brain substance. There were regional metastases to the lymph nodes of the hili of the kidney and also numerous but small pulmonary metastases, which were not visible in the chest plates even in retrospect after the diagnosis was known. Histologically, the lesion was somewhat peculiar in that the renal tumor was remarkably well differentiated and the metastases almost totally undifferentiated, so much so that at first there was some question whether we might be dealing with two tumors. Eventually, when all sections became available there were enough suggestive transition forms between the two types of tumor to make us believe that it all represented metastasis from the renal carcinoma.

We also found benign adenomas of the thyroid and adrenal glands, a fibroma of the ovary and numerous myomas of the uterus. None of these would have been the source of the metastatic disease. A terminal event, not reflected in the clinical picture, was a strangulation of the ileum with incipient gangrene due to old peritoneal adhesions. There was also some degree of organizing bronchopneumonia.

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Robert M. Green, M.D. Vernon P. Williams, M.D.
Dwight O'Hara, M.D. Benjamin Castleman, M.D.
Fletcher H. Colby, M.D. Hugh R. Leavell, M.D.
Robert L. Goodale, M.D. J. Englebert Dunphy, M.D.
Chester M. Jones, M.D. Charles H. Burnett, M.D.
Harvey R. Morrison, M.D. Theodore H. Ingalls, M.D.
Maxwell Finland, M.D. Deering G. Smith, M.D.*
*Representing the New Hampshire Medical Society.

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RESIGNATION OF DR. CLIFTON T. PERKINS

The resignation of Dr. Clifton T. Perkins as commissioner of mental health poses a problem for all the citizens of the Commonwealth, but especially for the medical profession. The following question is not an overstatement of the problem: Is the vast therapeutic effort of the Department of Mental Health, which employs 8200 persons and costs the citizens a third of the annual State budget, to move forward or to become subverted by politics?

It is no reflection on the present administration to define this issue, which is inherent in the size of the Department, the millions of dollars involved in it and the jobs available, ranging from unskilled labor positions to those requiring the highest technical competence. This issue was raging in the years immediately preceding Dr. Perkins's appointment by former Governor Hurley.

If hard-pressed but short-sighted politicians are not to prevail to the damage of the patients, the Governor must find a new commissioner who will combine the zeal of the crusading doctor with the skill of the political strategist. Dr. Perkins combined these essential qualities in high degree. He took over a department that had become low in morale as a result of political interference. Appointed by a Democrat, he was reappointed by a Republican, Leverett Saltonstall. He held the Department together during the difficult war years, when money and personnel were scandalously short. After the war, he inspired a public opinion that the legislature could not ignore, and the budget of the Department rose from $17,000,000 to $31,000,000 between 1946 and 1950. Great personnel shortages were relieved, and, at the time of his resignation, he had already launched a campaign to remedy the major deficiency in the compensation of doctors and other medical personnel.

Dr. Perkins was criticized by some doctors for being too much of a politician and by politicians as being too much of a doctor. The Commonwealth has been fortunate that he was skilled in both fields. The State of Maryland, to which he has gone as commissioner of mental hygiene, will benefit from his dual skills.

He leaves behind him many monuments of his work: resident training programs throughout the Commonwealth; evaluation and utilization of various forms of shock therapy in the state hospitals; psychosurgery in some of the hospitals; research activities in Worcester, Boston, Grafton, Monson and Wrentham; and a greater public awareness of the problem of mental health. These things were not his work alone, of course, but he merits his full share of recognition for their accomplishment. He was the man who had to deal with the doctors, who do not understand politicians, and the politicians, who understand neither doctors nor their work and often have a low opinion, for historical reasons happily no longer applicable, of doctors in Government service.

Who is going to hold the fort? There will be great pressure on the Governor to appoint a commissioner who will open the doors to jobs and contracts to the politically hungry. Governor Dever has demonstrated an uncommon solicitude for the mentally ill and the mentally deficient. The program he has backed proves this. The question remains: What

will happen to the program, including $17,000,000 more for building, when it passes from the legislative to the realization stage?

The Governor will know, as he faces this pressure, that his fine record as a friend of the mentally ill is in the balance. He realizes, of course, that his duty requires him to find and appoint a commissioner who is an able psychiatrist and an able administrator. He also knows that the new commissioner should be freely given the opportunities to run a psychiatric program, opportunities for which Dr. Perkins often had to fight tooth and nail.

The Governor will be better able to resist the pressure of the politicians if the people of the Commonwealth, armed with knowledge of the issues at stake, help him by insisting that the Department of Mental Health is in the business of medicine and not politics.

In the task of informing the citizens of this matter, the first and highest responsibility is quite clearly that of the members of the medical profession.

WHERE IS THY STING!

In a letter that appears in the *London Lancet* of June 18, 1949, the author, R. J. Matthews, of Cardiff, an officer of the Welsh Board of Health, takes issue on certain matters with his colleague, Joseph V. Walker, medical officer of health of Darlington. Although the discussion centers on the care of the aged, the difference concerns the normality of death.

Dr. Walker, in a previous communication to the *Lancet* of May 14, disapproving of the "angle of morbidity and the treatment of disease" from which the problem of old age has been approached, at least in Great Britain, further states that "Old age is not in itself a disease, and there must be a normal old age — and for that matter a normal death — just as there is a normal childhood and a normal birth."

"But what," Dr. Matthews asks, "is normal death?" Accepting the dictionary definition of normal as "the average of observed phenomena," ("not deviating from an established norm," according to Webster) he suggests that a normal death might perhaps be one resulting from "0.3 parts cardiovascular disease, 0.15 parts cancer, 0.04 parts tuberculosis, 0.0002 parts violence and so on."

A birth may be considered as normal because it usually conforms to a common pattern and takes place ordinarily at a given age. The manner of death is a singularly individual affair, even if its results are always the same, as the results of birth are so different from each other.

Gradual decay might be said to result in a "normal" death, barring accident, but the process is not a particularly attractive one. The "ideal" death, in distinction from this, may be a matter of opinion. Dr. Matthews's own aspiration so far as his eventual taking off is concerned would be shared by many another. It is that of a former Lord Chief Justice who died just after he had hooked a salmon in his ninety-first year.

The layman occasionally — perhaps not sufficiently often — receives comfort in this particular problem from the physician, himself mortal and all too human. The evidence points toward an eventual separation from life that is usually without fear and without suffering, however much suffering might have preceded it. Perhaps these observations are sometimes conceived in wishful thinking, but there is the story of the martyr burning at the stake who laughed at his persecutors because his suffering was so much less than he had anticipated, and those who have been raised from the nearly dead have testified to the tranquillity that preceded the final loss of consciousness.

> He who died at Azan sends
> This to comfort all his friends: —

The manner of death may seem to vary as much as its etiology, but fundamentally all death is as normal as it is inevitable, even though it may result from a variety of causes and occur at any age that man may reach.

The courage with which it is faced depends on the courage with which life has been faced. The Lord Chief Justice would not have hooked his salmon had he not gone fishing.

FOR CONTROL OF CANCER

APRIL is the month in which the American Cancer Society conducts its annual drive for funds to help continue the fight against cancer. The Massachusetts Division of the Society has designated April 2 as Cancer Control Sunday, the first day of its campaign, which will continue through the month. Walter H. Trumbull, as state campaign chairman, will be assisted by religious, professional and civic leaders as vice-chairmen and by community chairmen who will work at the local level to make sure that every citizen of the Commonwealth is given the opportunity of contributing toward the state quota of $530,166.

The program for which support is asked emphasizes the vital purposes of research, education and service. Liberal aid is given to the world-renowned centers for cancer research in Massachusetts, one of the nation's focal points for this type of investigation. The educational campaign is aimed both at dissemination of knowledge of symptoms, that patients may seek medical advice in the early stages of cancer, when most good can be done, and at fostering a clear understanding of the nature and course of the disease, to overcome the unreasoning terror in which it is generally held. Finally, adequate care of patients with cancer is made possible by the funds collected in the drive.

Prompt and generous support may be expected of the citizens of Massachusetts, where the deaths from cancer now number approximately 8500 each year. The advances of medical science continue to increase the life span to a remarkable extent, but the problem posed by the disease that is one of the leading causes of death among the elderly remains unsolved. Until a cure for cancer — long hoped for and patiently sought — has been discovered, research, education and service represent the only weapons of control. The appeal of the American Cancer Society should receive a generous response from physicians and laymen alike.

THE AUXILIARY

THE venerable *Journal*, now either one hundred and twenty-two or one hundred and thirty-eight years old, depending on whether the Julian or the Gregorian calendar is consulted, welcomes a great, great, great granddaughter to the family fold. On March 1, 1950, Number 1 of Volume 1 of *The Auxiliary*, the official publication of the Woman's Auxiliary to the Massachusetts Medical Society, made its initial appearance on a somewhat troubled stage, not like a lion or even a lioness, nor yet exactly like a lamb. Possibly for a brief moment it was at least the very youngest member of the vast family of contemporary journals.

The Auxiliary, published through the kind offices of Massachusetts Medical Service, should be of great value to the Auxiliary, for an official publication always aids in the achievement of that solidarity so necessary to the functioning of any organization.

Its growth and development and its widening sphere of usefulness will be watched with kindly interest by great, great, great grandpapa.

The observation of the celebrated John Abernethy is true with respect to the application of the nitrate of silver — "Subdue local irritation, and regulate the action of the digestive system, and you control all controllable disease."

The degree of Doctor of Medicine was conferred on 42 graduates at the Commencement of the Medical College of Ohio, held in Cincinnati, March 5th. 27 of these belong to the State of Ohio, and 10 were from Indiana.

Boston M. & S. J., *March 27, 1850*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

CHASE — Gilman L. Chase, M.D., of Clinton, died on March 16. He was in his seventieth year.

Dr. Chase received his degree from Harvard Medical School in 1906. He was formerly associate medical examiner of the second district of eastern Worcester and was a member of the New England Obstetrical and Gynecological Society and a fellow of the American College of Surgeons and American Medical Association.

His widow, a daughter, three grandsons, a sister and a brother survive.

BOSTON MEDICAL LIBRARY

CURRENT EXHIBITION

The two cases in the rotunda of the Library contain a selection of material relating largely to the evolution of the printed book from the manuscript form and to the early history of medicine in Massachusetts.

Jacobus Forliviensis was a learned physician and philosopher who lived in Padua during the period of the late thirteenth and the early fourteenth centuries. He is famous for his commentaries on the works of Avicenna, Galen and Hippocrates. The first case contains a fine manuscript of about 1450, with commentaries on the tegni and microtegni of Galen. The incunabula shown are the commentaries on the generation of the embryo of Avicenna (Siena, 1485) and on the aphorisms of Hippocrates (Pavia, 1484). The books are tall, fine specimens, and it should be noted that there is only a period of about thirty-five years between the dates of the manuscript and those of the printed books. Early incunabula from presses at Pavia and Siena are uncommon. The Library also owns the *Expositio in primum librum Canonis Avicennae* (Pavia, 1500).

The history case contains a selection of important manuscripts, comprising the original medical directions of Governor John Winthrop, of Massachusetts Bay Colony, dated 1643. It was written in London, by Ed. Stafford, probably at the request of the Governor, and sent to him in Boston for use in the physical care of his constituents. The manuscript was published with notes by Dr. Oliver Wendell Holmes, in the *Proceedings of the Massachusetts Historical Society* in 1862, and reprinted in pamphlet form.

John Winthrop, the younger, son of the Massachusetts governor, was a learned man, a physician and scientist. He was governor of Connecticut for nineteen years. The Library has a collection of twenty-eight letters written to him by various persons seeking his advice in medical matters.

John Denison Hartshorn was apprenticed to the famous Dr. Silvester Gardiner, of Boston, and a student in physic during the years 1753-1756. He worked in the apothecary shop and attended the poorer patients and the soldiers in the garrison. He kept a complete diary, day by day, of his doings, even including his meals, and died in May, 1756, at the age of twenty years and six months, during a prevailing epidemic. The final entry in his diary "I am prodigious tired going about all day" might well constitute a fitting epitaph for his tomb. The diary is an important document from a medical and sociologic point of view. Also, there are the formulary of Elijah Dix, of Boston, dated 1768, and the *Present State of America* (1776), by Thomas Thaxter, of Hingham, Massachusetts.

The printed material includes complete copies of the first two medical books printed in the United States, both done at Boston, and both by Nicholas Culpepper, of London: *The English Physician* (Boston, 1708) and the *Pharmaecopeia Londoniensis* (Boston, 1720).

There are also shown a *Catalogue of Drugs and Medicine, Instruments and Utensils, Dye-Stuffs, Groceries, and Painter's Colours, Imported, Prepared and Sold*, by Smith and Bartlett (Boston, 1795); the *Catechism of Health*, by B. C. Faust, M.D. (Boston, 1795); and two important books of Dr. John Morgan, of Philadelphia, an autographed copy of his *Discourse upon the Institution of Medical Schools in America* (Philadelphia, 1765), said to constitute the beginning of medical education in the United States, and the *Vindication of His Public Character* in the *Station of Director-General of the Military Hospitals and Physician-in-Chief to the American Army, anno 1776* (Boston, 1777). This last is an important and valuable piece of Americana. The catalogue of the drugstore of 1795 suggests that there is nothing new in the drugstore of today.

NEW HAMPSHIRE MEDICAL SOCIETY

OBITUARY

Dr. Howard N. Kingsford, former medical director at Dartmouth College and emeritus professor of pathology and bacteriology at Dartmouth Medical School, died on February 15, 1950, after several months' illness. He was seventy-eight years of age.

After the reorganization of the New Hampshire Board of Registration in 1915, Dr. Kingsford served as chairman or president of the State Licensing Board for Physicians for thirty-three years.

Born in Providence, Rhode Island, on September 24, 1871, Dr. Kingsford received his degree from Dartmouth Medical School in 1898. From 1898 to 1901, he was instructor in histology, bacteriology and pathology at Dartmouth Medical School, and in 1901 he was named professor of pathology and bacteriology, the position he held until his retirement in 1941. He had also studied medicine in Europe and was awarded an honorary master's degree by Dartmouth in 1907.

Dr. Kingsford was known to thousands of Dartmouth men as medical director of the college, a post he held from 1919 to 1941. Before the adoption of the present college health service and the building

of the Dartmouth infirmary, he was responsible for the isolation of all students with contagious diseases.

Dr. Kingsford had also served as a pathologist at the Mary Hitchcock Memorial Hospital and as New Hampshire state bacteriologist. He was a member of the American Association of Pathologists and Bacteriologists, the New Hampshire Medical Society and the New Hampshire Surgical Club and a fellow of the American Medical Association. During World War I, he was a captain in the Army Medical Corps.

In 1942, he was elected to the New Hampshire House of Representatives.

Dr. Kingsford was an ardent amateur horticulturist, and several of the flowers he raised were awarded prizes in various garden shows.

In 1898, he was married to Mable P. Carpenter, of Boston, Massachusetts, who died in 1922.

In 1923, he was married to Harriet W. Horton, who survives him. He also leaves a sister, Mrs. William E. Westfield of Riverside, Rhode Island, and five brothers, Arthur H. Kingsford and Frank W. Kingsford, both of Riverside, Blanding C. Kingsford, of San Diego, California, Carleton L. Kingsford, of East Wakefield, and Winthrop Kingsford, of East Haven, Connecticut.

R. W. T.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR FEBRUARY, 1950

RÉSUMÉ

Diseases	February 1950	February 1949	Seven-Year Median
Chancroid	2	8	2*
Chicken pox	2043	3776	1838
Diphtheria	13	32	21
Dog bite	584	665	564
Dysentery, bacillary	6	0	9
German measles	143	207	188
Gonorrhea	182	203	345
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	0	1*
Malaria	0	0	8
Measles	611	5285	2021
Meningitis, meningococcal	6	4	19
Meningitis, Pfeiffer-bacillus	4	5	2
Meningitis, pneumococcal	5	2	2
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	2	1	5
Mumps	916	1301	1113
Poliomyelitis	0	0	0
Salmonellosis	4	2	4
Scarlet fever	509	1312	1201
Syphilis	94	168	351
Tuberculosis, pulmonary	250	183	192
Tuberculosis, other forms	15	10	13
Typhoid fever	3	4	2
Undulant fever	1	2	1
Whooping cough	518	249	410

*Six-year median.

COMMENT

Diseases above the seven-year median were chicken pox, dog bite, pulmonary tuberculosis and whooping cough.

Diseases below the seven-year median were diphtheria, German measles, measles, mumps and scarlet fever.

Whooping cough was more prevalent than it had been since 1947; for the twelfth consecutive month cases exceeded the number for the same month the previous year.

No cases of poliomyelitis were reported this month. Measles was at the lowest level since 1919, with the exception of February, 1945, when only 305 cases were reported. This was the eighth month in which scarlet fever remained below the seven-year median; only once since 1906 had February shown a lower prevalence.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from: Boston, 4; Blackstone, 1; Cambridge, 1; Everett, 3; Halifax, 1; Somerset, 1; Somerville, 1; Tewksbury, 1; total, 13.

Dysentery, bacillary, was reported from: Belchertown, 3; Newton, 1; Worcester, 2; total, 6.

Encephalitis, infectious, was reported from: Canton, 1; Shrewsbury, 1; Worcester, 1; total, 3.

Infectious hepatitis was reported from: Wellesley, 1; Wrentham, 2; total, 3.

Meningitis, meningococcal, was reported from: Belchertown, 1; Boston, 1; Brockton, 2; Gardner, 1; Winchester, 1; total, 6.

Meningitis, Pfeiffer-bacillus, was reported from: Boston, 1; Mansfield, 1; Westwood, 1; Winchendon, 1; total, 4.

Meningitis, pneumococcal, was reported from: Fitchburg, 1; Hatfield, 1; Haverhill, 1; Mansfield, 1; New Bedford, 1; total, 5.

Meningitis, mumps, was reported from: Braintree, 1; Wrentham, 1; total, 2.

Meningitis, undetermined, was reported from: Ayer, 1; Weymouth, 1; total, 2.

Salmonellosis was reported from: Boston, 1; Brookline, 1; Cambridge, 1; Newbury, 1; total, 4.

Septic sore throat was reported from: Adams, 1; Boston, 3; Foxboro, 1; Worcester, 1; total, 6.

Trichinosis was reported from: Boston, 1; total, 1.

Typhoid fever, was reported from: Brockton, 1; Middleboro, 1; Nantucket, 1; total, 3.

Undulant fever was reported from: Uxbridge, 1; total, 1.

MISCELLANY

JOURNAL OF THE PHILADELPHIA GENERAL HOSPITAL

The first issue of the *Journal of the Philadelphia General Hospital*, a quarterly published by the Philadelphia General Hospital, has appeared. It is edited by Dr. P. F. Lucchesi, superintendent and medical director, with a consulting board of editors including Drs. William P. Boger, Jefferson H. Clark, William E. Ehrich, Thomas M. McMillan, John F. Stouffer and B. P. Widmann.

Copies may be obtained from Dr. S. O. Waife, associate editor.

CORRESPONDENCE

INDUSTRIAL ACCIDENT BOARD ADOPTS NEW FEE SCHEDULE

To the Editor: The Industrial Accident Board has by vote passed on Monday, March 6, 1950, established the fee for office visits in industrial-accident cases at $3.00. This rate will apply to such visits made on and after March 6, 1950. For some short time prior to March 6, the rate has been $2.50 having been raised to that rate from $2.00, which was the rate for many years previously.

Dr. William E. Browne, secretary to the Medical Advisory Committee of the Industrial Accident Board, suggested that publication in the *Journal* would bring this matter to the

attention of physicians generally. We, of course, are circularizing all insurers, self-insurers and compensation agents in the Commonwealth, counties, cities, towns and districts charged with the administration of workmen's compensation benefits by such political subdivisions in cases within their respective jurisdictions.

EDWARD DOYLE, *Secretary*

Boston, Massachusetts

NEW ENGLAND CHAPTER OF ARTHRITIS AND RHEUMATISM FOUNDATION

To the Editor: One of the declared functions of the New England Chapter of the Arthritis and Rheumatism Foundation is to promote better medical and public understanding of the rheumatic diseases. Although this does not imply that the Foundation is called upon to make known an assessment of every new method of therapy in such conditions, glaringly misleading advertising to profession and public of products that seemingly bear the stamp of scientific approval should not be allowed to pass unchallenged. Such a product is Glucurone (glucuronolactone), recently given wide publicity both to doctors through the mails and to the laity through press releases. At a meeting of the Medical and Scientific Committee of the New England Chapter of the Foundation held on January 21, 1950, it was voted that a communication regarding the status of Glucurone as a therapeutic agent in arthritis be sent to the medical journals published in the New England area.

The advertising matter in this instance has been cleverly composed in a way to lead the casual reader to conclude that glucuronic acid deficiency is of basic importance in the pathogenesis of the rheumatic diseases, that glucuronic acid may have an important remedial role in these conditions as a detoxifying agent and that notable therapeutic success has been obtained in carefully controlled studies by the use of Glucurone in various forms of arthritis. None of these conclusions are upheld by scientific or clinical observations to date.

In one brochure circulated to the medical profession and in certain press releases, references to ACTH and Cortisone are carefully worded and so appropriately placed as to imply that Glucurone is the next best therapeutic agent and has the obvious advantages of being more readily available and much less expensive. As far as rheumatoid arthritis is concerned, essentially negative results have been obtained in the treatment of 20 patients with Glucurone by the Arthritis Clinic of the Massachusetts General Hospital, Boston. Unpublished results from other large clinics are in agreement.

For the reasons stated above, the Committee considers itself justified in advising the medical profession that no basis has yet been established for the introduction of Glucurone as a remedy in the rheumatic diseases.

For the Committee: Sven M. Gundersen, M.D.
Francis C. Hall, M.D.
Charles L. Short, M.D.
Charles W. Steele, M.D.
Hiram E. Upton, M.D.

HANS WAINE, M.D.
Medical Director
New England Chapter
Arthritis and Rheumatism Foundation

LECTURE ON ATOMIC ENERGY

To the Editor: On Thursday, April 27, at 8 p.m., the twelfth in a special series of lectures sponsored by the Medical Units of the 94th Infantry Division will be presented in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston. The subject will be "Medical Aspects of Atomic Energy," and will be based on material condensed from the full five-day course on this subject given by the Army Medical Department Research and Graduate School in Washington, D. C.

This lecture is of timely interest to all physicians whether members of reserve components or not. In fact, it is an unusual opportunity for all interested physicians to obtain the pertinent material on this important subject in one session.

The implications of atomic destruction should, of course, be obvious to all thinking physicians, who are urged to avail themselves of this opportunity for proper introduction and orientation in this new weapon and its biologic effects.

In the absence of any formal radiologic defense program at the present time, it behooves all physicians at least to have accurate information on this subject and the possible role they may have to take in the future. The speaker will be Benjamin Bell, M.D. (Major, M.C., Res.) of the Eye, Ear, Nose and Throat Department of the Veterans Administration in Boston. Dr. Bell has attended the course at the Army Medical Center and has expended much time and effort in organizing the pertinent material for an interesting and instructive presentation in a single session. His prior lectures to military and Veterans Administration medical groups have been exceptionally well received and favorably commented upon.

The lecture will start with an introduction to radioactivity, both natural and artificial, and will include the concepts of nuclear fission and nuclear synthesis, the former being the basis of the atomic pile and the atomic bomb, and the latter being the theoretical basis for the hydrogen bomb. This will be followed by an explanation of certain bomb phenomena of tissue injury due to blast and heat. A presentation of radiation sickness and death including investigative lines of treatment will conclude the major portion of this session. A question period will be provided for, and if time permits, a suitable film will be shown.

WILLIAM H. CHASEN, M.D
Lieutenant Colonel, M.C., Res.
Division Surgeon, 94th Infantry Division
Army Base, Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Physiology in Diseases of the Heart and Lungs. By M.D. Altschule, M.D., assistant professor of medicine, Harvard Medical School, visiting physician and research associate, Beth Israel Hospital, and director of internal medicine and of research in clinical physiology, McLean Hospital. 8°, cloth, 368 pp. Cambridge: Harvard University Press, 1949. $5.00. Harvard University Monograph in Medicine and Public Health Number 10.

This monograph provides a complete systematic and critical review of the literature on the subject. Theoretical considerations have not been emphasized, but the facts are allowed to speak for themselves. Extensive bibliographies are appended to the various chapters, and the bibliography as a whole is practically unique, since it comprises as far as possible all the literature on the subject. The contents of the book served as a basis for the lectures given by the author to third-year and fourth-year medical students over a period of several years. The volume is well published in every way and should be in all medical libraries and available to all persons interested in the subject.

Gynaecological Histology. By Josephine Barnes, M.A., D.M. (Oxford), M.R.C.P. (London), F.R.C.S. (England), M.R.C.O.G., assistant, Obstetric Unit, University College Hospital, London, assistant obstetrician and gynecologist, Elizabeth Garrett Anderson Hospital, and surgeon, Marie Curie Hospital. 8°, cloth, 242 pp., with 162 illustrations. New York: Grune and Stratton, 1949. $6.50.

This small atlas consists of photomicrographs of slides of normal and diseased tissues. It is based on two previous catalogues of slides prepared for medical students. The text has been kept as clear and simple as possible, and for this reason references to the literature have been omitted. It is assumed that the user of the book has a knowledge of normal and pathologic anatomy and histology, and of clinical gynecology and endocrinology. The book is well published, and the plates are excellent, and it should prove useful to students of the subject. The printing was done in England.

German-English Medical Dictionary. Compiled by F. S. Schoenewald, M.D., Berlin. 8°, cloth, 241 pp. Philadelphia: Blakiston Company, 1949. $8.50.

This new medical dictionary is not merely a list of words but might be characterized as a phrase book. A great many of the words defined are not medical words but are words commonly met with in everyday reading of German medical literature. The book is a welcome addition to its field, although it cannot be expected to supersede Lang as a German-English medical dictionary. However, it should be added to the dictionary collection of all medical and scientific libraries.

Nervous and Neurohumoral Regulation of Intestinal Motility. By W. B. Youmans, professor of physiology, University of Oregon Medical School. 8°, cloth, 129 pp., with 32 illustrations. New York: Interscience Publishers, Incorporated, 1949. $4.75. (Monographs in the Physiological Sciences.)

This monograph summarizes present knowledge concerning the role of the extrinsic nerves of the small intestine in the regulation of intestinal motility. It is based on twelve years' work on the subject. Bibliographies are appended to the various chapters. The small volume is well published in every way, except for the omission of indexes of authors and subjects. The seemingly high price for such a small volume evidently reflects the estimate of its distribution. It should be in all collections on digestive diseases and physiology.

Blood: The Journal of Hematology. Vol. IV, No. 5. May, 1949. 4°, paper, 696 pp. New York: Grune and Stratton, 1949. $3.75.

This special number by twenty-three specialists constitutes a symposium on the blood cells and their reactions. Two years ago, a special number was published and was sold at an additional price outside the subscription price. This practice evoked considerable criticism on the part of subscribers to the journal, and with this criticism in mind the present special number was issued to subscribers without additional cost. However, this number may be purchased separately at the indicated price.

Life Among Doctors. By Paul de Kruif, Ph.D. In collaboration with Rhea de Kruif. 8°, cloth, 470 pp. New York: Harcourt, Brace and Company, 1949. $4.75.

Dr. de Kruif has previously written ten popular medical books. This last volume of the series is autobiographic and in addition, presents semi-biographic sketches of outstanding physicians who have made outstanding contributions to medicine during the period from 1940 to 1948, on public health, group medical service, vitamins, the one-day treatment of syphilis, venereal disease, rheumatic heart disease, subacute bacterial endocarditis, myasthenia gravis and cancer. The text is written in an interesting, sketchy manner. The book is well published and has a good index. It merits a place in medical-history collections and in public libraries.

Atomic Medicine. Edited by Charles F. Behrens, M.D., Captain, MC, United States Navy, director, Atomic Defense Division, Bureau of Medicine and Surgery, Navy Department, and medical officer in command, Naval Medical Research Institute, National Medical Center, Bethesda, Maryland. 8°, cloth, 416 pp., with illustrations and tables. New York: Thomas Nelson and Sons, 1949. $7.50.

Twenty specialists, physicians and scientists, many of them members of the Army, Navy and atomic services, have collaborated in writing this much needed book on an important new subject. The whole field of atomic energy, as related to medicine and the allied sciences, is covered, including the physics of the atom family, the biology, hematology, cumulative effects and permissible dosage limits of ionizing radiations, the pathological anatomy of total body irradiation, radiation illness and the various biologic and therapeutic aspects of radioactive isotopes, including radiophosphorus and radioiodine. Two appendixes comprise a long isotope table, and a list of selected technical symbols, units and definitions. A list of pertinent references is appended to each chapter. The book is well published and should be in all medical libraries.

Oral Bacterial Infection: Diagnosis and treatment. By Lyon P. Strean, M.Sc., Ph.D., D.D.S., F.A.P.H.A., director of Research Novocol Chemical Manufacturing Company, Incorporated, Brooklyn, New York. 8°, cloth, 185 pp., with 57 illustrations. Brooklyn: Dental Items of Interest Publishing Company, Incorporated, 1949. $5.50. (Modern Dentistry Series.)

This book is intended as a ready-reference text for medical and dental students and is based on the lectures given by the author over a number of years. Particular attention is given to dental caries and diseases beginning in the oral cavity or communicated by oral secretions. Some of the author's work with the lactobacillus and with *Haemophilus pertussis* is included in the proper place in the text. Different chapters are devoted to the various bacilli. There are also special chapters on the higher bacteria, the spirochetes, vibrios, rickettsia, fungi, protozoa, viruses and antibiotics, and on immunity. Emphasis is placed on diagnosis and treatment.

Streptomycin and Dihydrostreptomycin in Tuberculosis: Reports of research including studies sponsored by the American Trudeau Society (Medical Section, National Tuberculosis Association). Edited by H. McLeod Riggins, M.D., and H. Corwin Hinshaw, M.D. 8°, cloth, 554 pp., with illustrations and tables. New York: National Tuberculosis Association, 1949. $7.50.

This composite volume, the work of fifty-eight collaborators, is based on reports made to six manufacturing chemical and pharmaceutical firms who donated $1,000,000 worth of streptomycin for research purposes. These reports were enlarged, revised and brought up to date on the use of the streptomycins, para-aminosalicyclic acid and the sulfones, in combination with the streptomycins in the treatment of all forms of tuberculosis, to form the present volume. The first chapter presents early experimental and clinical studies made by a number of physicians in 1944 and 1945. Lists of selected references are appended to the various chapters. The book is recommended for all medical libraries and to all physicians interested in tuberculosis.

Photoradiography in Search of Tuberculosis. By David Zacks, M.D., chief of clinics, Massachusetts Department of Public Health. 4°, cloth, 297 pp., with 274 illustrations. Baltimore: Williams and Wilkins Company, 1949. $5.00.

This special monograph is divided into two parts. The first is devoted primarily to consideration of "mass chest radiography" and related technics, their organization, operation and value. The second comprises an atlas of 254 chest photoradiograms. The final chapters describe promotional and educational materials, and record forms and reports. The work is based on twenty years' experience with mass tuberculin testing and x-ray examinations conducted by the author for the Massachusetts Department of Public Health. The book is well published and should be in all medical libraries and in all collections on public health and tuberculosis. The price is reasonable, considering the large number of special illustrations used in the volume.

Blood and Plasma Transfusions. By Max M. Strumia, M.D., Sc.D. (Med.), associate professor of pathology, Graduate School of Medicine, University of Pennsylvania, and director, Laboratory of Clinical Pathology, and of the John S. Sharpe Research Foundation, Bryn Mawr Hospital; and John J. McGraw, Jr., M.D., instructor in pathology, Graduate School of Medicine, University of Pennsylvania, and assistant attending pathologist, Bryn Mawr Hospital. 8°, cloth, 497 pp., with 124 illustrations. Philadelphia: F. A. Davis Company, 1949. $7.50.

In this book the authors have covered all the aspects of the subject — clinical, pathological and technical. Lists of selected references are appended to the various chapters. The type and printing are excellent, but the use of a coated paper is not justified by the kind or number of the illustrations. The book is comprehensive in scope and should be in the reference collections of all medical libraries and available to all persons interested in the subject.

NOTICES

ANNOUNCEMENTS

Dr. Eugene Guralnick announces that his office for the practice of medicine is still at 422 Beacon Street, Boston.

Dr. James A. Halsted, Boston, has resigned as chief of the Medical Service of the Faulkner Hospital to accept a full-time position as section chief in the Wadsworth Veterans Administration Hospital, Los Angeles 25, California.

WOMAN'S AUXILIARY TO SUFFOLK DISTRICT MEDICAL SOCIETY

The annual meeting of the Woman's Auxiliary to Suffolk District Medical Society will be held at the Boston Medical Library, 8 the Fenway, on Wednesday, April 5, at 1 p.m. This is to be a buffet luncheon meeting, and after the meeting, Dr. Raymond J. Dillon, photographer on Captain Irving Johnson's globe-circling voyages aboard the schooner Yankee, will show some of his pictures taken on that expedition.

Reservations for the luncheon, at $0.99 each, should be made with Mrs. Merrill C. Sosman, 24 Lee Road, Chestnut Hill, by Monday, April 3.

Members of the Auxiliary have the privilege of bringing to this meeting any eligible guests from their districts.

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The Yearly Meeting and Dinner of the Massachusetts Society of Examining Physicians will be held at the Harvard Club of Boston, on Wednesday, May 10, at 6 p.m.

94TH INFANTRY DIVISION LECTURE

The twelfth lecture in the series sponsored by the 94th (Bay State) Division will be held in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston, on Thursday, April 27, at 8 p.m.

Dr. Benjamin Bell will speak on the subject "Medical Results of Atomic Energy."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit if authorized by the instructor of their unit of assignment. If time permits, excellent films will be shown during this period.

MASSACHUSETTS CHAPTER OF AMERICAN ACADEMY OF GENERAL PRACTICE

The 1950 spring clinical session of the Massachusetts Chapter of the American Academy of General Practice will be held in Boston on Wednesday, May 10. The morning program will take place at the New England Medical Center, Harrison Avenue, at Bennet Street. The business meeting will be followed by a series of clinics under the direction of Dr. Samuel H. Proger, medical director of the Center.

The luncheon, afternoon lectures, dinner and evening entertainment will be at the Hotel Puritan. The speaker of the evening will be Rudolph Elie, roving reporter and music critic of the *Boston Herald*. There will be an afternoon program for the ladies.

A block of tables has been reserved at Symphony Hall for the Boston Pops concert on Tuesday evening, May 9.

AMERICAN ACADEMY OF NEUROLOGY

The first interim meeting of the American Academy of Neurology will be held in Cincinnati on April 14 and 15. The meeting is being held in conjunction with the American Chapter of the International League Against Epilepsy, which will meet on April 15 and 16. On April 15 there will be a joint meeting between the two societies and a large symposium on psychomotor epilepsy.

SOCIETY MEETINGS AND CONFERENCES

October 3–May 19. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 286, issue of August 18.

January 9–December 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.

April 1. Springfield Hospital. Page 488, issue of March 23.

April 3. New England Cardiovascular Society. Page 488, issue of March 23.

April 3. Hartford Medical Society. Page 386, issue of March 9.

April 3 and 4. American College of Surgeons. Page 427, issue of March 16.

April 4. Boston City Hospital House Officers' Association. Page 487, issue of March 23.

April 5. Woman's Auxiliary to Suffolk District Medical Society. Notice above.

April 6. New England Hospital for Women and Children. Page 488, issue of March 23.

April 7. Public Seminar in Chemotherapy. Page 270, issue of February 16.

April 10. Boston Chapter of the American Federation for Clinical Research, Beth Israel Hospital, Boston. 8:00 p.m.

April 10 and 11. American College of Surgeons. Page 427, issue of March 16.

April 13. The Value of the Bone Bank. Dr. Joseph H. Shortell. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

April 14 and 15. American Academy of Neurology. Notice above.

April 15. Springfield Hospital. Page 488, issue of March 23.

April 17. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.

April 17. Hartford Medical Society. Page 386, issue of March 9.

April 18. Springfield Hospital. Page 488, issue of March 23.

April 19. Tufts Medical Alumni Association. Page 488, issue of March 23.

April 21. National Rehabilitation Association. Page 488, issue of March 23.

April 21. Sixtieth Anniversary of Clark University. Page 428, issue of March 16.

April 22–29. American Association of Industrial Physicians and Surgeons. Page 305, issue of February 23.

April 24–28. National Tuberculosis Association. Page 678, issue of October 27.

April 25–28. Philadelphia County Medical Society. Page 386, issue of March 9.

April 26. New England Obstetrical and Gynecological Society. Rhode Island Hospital and Providence Lying-in Hospital, Providence, Rhode Island.

April 27. 94th Infantry Division Lecture. Notice above.

April 29. Eastern Section of American Congress of Physical Medicine. Page 306, issue of February 23.

April 29. Long Island College of Medicine Alumni Day. Page 348, issue of March 2.

May 3. Norfolk District Medical Society Anniversary Dinner.

May 3–7. Second European Congress of National Associations of Gastroenterology. Page 428, issue of March 16.

May 4. Suffolk District Censors' Meeting. Page 234, issue of February 9.

May 10. Massachusetts Society of Examining Physicians. Notice above.

May 10. Massachusetts Chapter of American Academy of General Practice. Notice above.

May 14–19. International and Fourth American Congress of Obstetrics and Gynecology. Page 160, issue of January 26.

May 16–18. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

May 17. Luncheon Meeting. Section on Diseases of the Eye, Ear, Nose and Throat, Massachusetts Medical Society. Hotel Statler, Boston. 12:00 m.

May 22 and 23. National Research Council Committee on Human Reproduction. Page 488, issue of March 23.

May 24–26. American Association of Genito-Urinary Surgeons. Page 234, issue of February 9.

June 22–25. American College of Chest Physicians. Page 270, issue of February 16.

June 24 and 25. American Society for the Study of Sterility. Page 38, issue of January 5.

June 26–30. American Physicians Art Association. Page 428, issue of March 16.

June 26–30. American Medical Association. Annual Session. San Francisco, California.

July 17–22. International Congress for Scientific Research. Page xvii, issue of September 1.

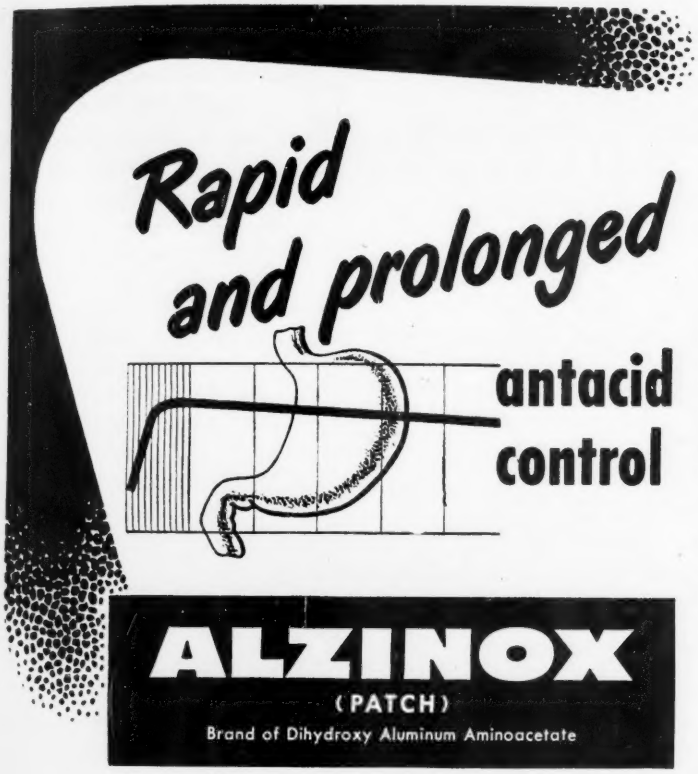
August 21–26. International Society of Hematology. Page 888, issue of December 1.

August 28–September 1. American Congress of Physical Medicine. Page 428, issue of March 16.

August 31–September 7. World Federation for Mental Health. Page 306, issue of February 23.

September 3–9. International Heart Congress. Page 160, issue of January 26.

(*Notices concluded on page xv*)



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NOTICES (*Concluded from page 528*)

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.
OCTOBER 12–14. American Association of Blood Banks. Page 428, issue of March 16.
NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

DISTRICT MEDICAL SOCIETIES

NORFOLK
MAY 3. Anniversary Dinner.

SUFFOLK
APRIL 5. Woman's Auxiliary.
MAY 4. Censors' Meeting.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 6

THURSDAY, APRIL 6
*9:00–10:00 a.m. Cardiac Grand Rounds. Main Amphitheater, Children's Medical Center.

FRIDAY, APRIL 7
*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

MONDAY, APRIL 10
*11:30 a.m.–12:15 p.m. Chest X-Ray Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*8:00 p.m. Boston Chapter of the American Federation for Clinical Research. Beth Israel Hospital, Boston.

TUESDAY, APRIL 11
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, APRIL 12
*11:00 a.m.–12:00 m. Medical Rounds. Children's Medical Center.
*12:00 m. Clinicopathological Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Medical Center). Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined Clinic of all Medical Center Services. Amphitheater, Children's Hospital.

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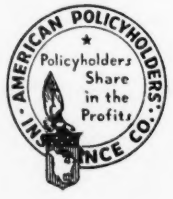

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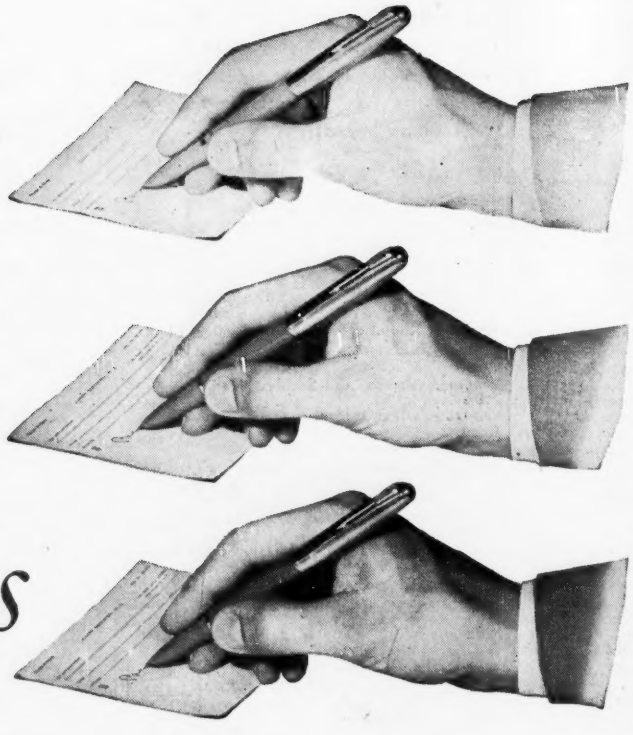

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